P. ENT COOPERATION TRE. Y

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

CURTIS, Philip, Anthony
A.A. Thornton & Co.
235 High Holborn
London WC1V 7LE
ROYAUME-UNI

Date of mailing (day/month/year)
01 February 2001 (01.02.01)

Applicant's or agent's file reference
PAC/19599

International application No.
PCT/GB00/02128

IMPORTANT NOTIFICATION

International filing date (day/month/year)
02 June 2000 (02.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

REGEN THERAPEUTICS PLC
88 Kingsway
London WC2B 6AA
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

REGEN THERAPEUTICS PLC
Suite 406
Langham House
29-30 Margaret Street
London W1W 8SA
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Christine Carrié
Telephone No.: (41-22) 338.83.38

003812778

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 January 2001 (23.01.01)	
International application No. PCT/GB00/02128	**Applicant's or agent's file reference** PAC/19599
International filing date (day/month/year) 02 June 2000 (02.06.00)	**Priority date** (day/month/year) 02 June 1999 (02.06.99)
Applicant GEORGIADES, Jerzy, A.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 December 2000 (22.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

GB0002128

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PAC/19599		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/02128	02/06/2000	02/06/1999
Applicant		
REGEN THERAPEUTICS PLC		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   PEPTIDE FRAGMENTS OF COLOSTRININ

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
GB 00/02128

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-32(all partially), 33-35(complete)

   Peptides having the structure defined by SEQ ID No 1, 7 or 16, peptides containing them, their compositions and use and antibodies to said peptides

2. Claims: 1-32(partially)

   Peptide having the structure defined by one of the SEQ ID No 2-6 and 8, peptides containing it, their compositions and use and antibodies to said peptides

3. Claims: 1,3-5,7-32(partially)

   Peptide having the structure defined by one of the SEQ ID No 9-15,17 and 18, peptides containing it, their compositions and use and antibodies to said peptides

4. Claims: 1,3-5,7-32(partially)

   Peptide having the structure defined by one of the SEQ ID No 19-32, peptides containing it, their compositions and use and antibodies to said peptides

5. Claims: 1,3-5,7-32(partially)

   Peptide having the structure defined by the SEQ ID No 33, peptides containing it, their compositions and use and antibodies to said peptides

International Application No
PCT/GB[redacted]/02128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 A23L1/305 A61K38/17 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, MEDLINE, WPI Data, PAJ, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 14473 A (GEORGIADES BIOTECH LTD ;JANUSZ MARIN (PL); LISOWSKI JOZEF (PL); DU) 9 April 1998 (1998-04-09) cited in the application the whole document ---	1,2,4-6, 9-32
X	JUNG E.A.: "Peptides 1988, Proceedings 20th EPS,1988, Tübingen" 1989 , WALTER DE GRUYTER , BERLIN XP002148606 page 742 -page 744 --- -/--	1,4-6, 9-32

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" eartier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2000	03. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB[redacted]/02128

C.(Continuation) DOCUMENTS CONSIDERED TO [redacted]LEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SLOOTSTRA J W ET AL: "STRUCTURAL ASPECTS OF ANTIBODY-ANTIGEN INTERACTION REVEALED THROUGHSMALL RANDOM PEPTIDE LIBRARIES" MOLECULAR DIVERSITY,NL,ESCOM SCIENCE PUBLISHERS, LEIDEN, vol. 1, 1996, pages 87-96, XP002051008 ISSN: 1381-1991 the whole document ---	1,3-5,7, 22,23
X	BREZDEN E.A.: "FMRFamide-activated Ca2+ channels in Lymnaea heart cells are modulated by SEEPLY, a neuropeptide encoded on the same gene" J.NEUROPHYSIOL, vol. 81, no. 4, April 1999 (1999-04), pages 1818-1826, XP002155471 page 1818, column 2 ---	1,4,5, 9-27,31, 32
X	PAUCHA E.A.: "Immunoprecipitation of some forms of simian virus 40 large T antigen by antibodies to synthetic peptides" JOURNAL OF VIROLOGY., vol. 51, no. 3, September 1984 (1984-09), pages 670-681, XP000971425 AMERICAN SOCIETY FOR MICROBIOLOGY US See Fig.1, peptide A ---	1,4,5, 9-18, 22-27, 31,32
X	KIM E.A.: "A novel member of the RING finger family, KRIP-1" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, December 1996 (1996-12), pages 15299-15304, XP002155473 WASHINGTON US See Fig.2, (aa.500-505) ---	2,4,6
X	DATABASE WPI Section Ch, Week 199423 Derwent Publications Ltd., London, GB; Class B04, AN 1994-188987 XP002155476 & JP 06 128287 A (NISSHIN FLOUR MILLING CO), 10 May 1994 (1994-05-10) abstract ---	1,3-5,7, 9-19, 21-27
X	DATABASE WPI Section Ch, Week 199411 Derwent Publications Ltd., London, GB; Class B04, AN 1994-089332 XP002155477 -& JP 06 041191 A (CALPIS SHOKUHIN KOGYO KK), 15 February 1994 (1994-02-15) abstract ---	1,3-5, 7-18, 22-27

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International Application No
PCT/GB[redacted]/02128

C.(Continuation) DOCUMENTS CONSIDERED TO [redacted]LEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 24371 A (MIDIA LIMITED ;POZZILLI PAOLO (IT)) 10 July 1997 (1997-07-10) The whole document; see especially SEQ ID NO 6	1,3-5,7, 9-18, 22-30
X	DATABASE WPI Section Ch, Week 199651 Derwent Publications Ltd., London, GB; Class B04, AN 1996-515013 XP002155478 & JP 08 269090 A (SNOW BRAND MILK PROD CO LTD), 15 October 1996 (1996-10-15) abstract	1,3-5,7, 9-19, 21-27
X	EP 0 583 074 A (CALPIS FOOD IND CO LTD) 16 February 1994 (1994-02-16) the whole document	1,3-5, 7-18, 22-27
X	OTANI H ET AL: "THE COMMON ANTIGENIC SITE OF BOVINE AND HUMAN BETA-CASEINS" MILCHWISSENSCHAFT,VV GMBH VOLKSWIRTSCHAFTLICHER VERLAG. MUNCHEN,DE, vol. 43, no. 11, 1988, pages 705-707, XP000952715 ISSN: 0026-3788 the whole document	1,3-5, 7-18, 22-27
X	DATABASE WPI Section Ch, Week 199015 Derwent Publications Ltd., London, GB; Class B04, AN 1990-111933 XP002155479 -& JP 02 062828 A (AJINOMOTO KK), 2 March 1990 (1990-03-02) abstract	1,3-5, 7-18, 22-27
A	GIDROL E.A.: "Annexin-like protein from Arabidopsis thaliana rescues delta-oxyR mutant of E coli from H2O2 stress" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, October 1996 (1996-10), pages 11268-11273, XP002155474 WASHINGTON US figure 3	1,3-5,7, 8

-/--

International Application No
PCT/GB[redacted]/02128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PROVOT C ET AL: "Complete sequence of the ovine beta-casein-encoding gene and interspecies comparison" GENE,NL,ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, vol. 154, no. 2, 1995, pages 259-263, XP004042484 ISSN: 0378-1119 figure 1 ---	
A	CARLES E.A.: "A new strategy for primary structure determination of proteins: application to bovine beta-casein" FEBS LETTERS, vol. 229, no. 2, March 1988 (1988-03), pages 265-272, XP002155475 AMSTERDAM NL the whole document ---	
A	GREENBERG R ET AL: "HUMAN BETA-CASEIN. AMINO ACID SEQUENCE AND IDENTIFICATION OF PHOSPHORYLATION SITES" JOURNAL OF BIOLOGICAL CHEMISTRY. (MICROFILMS),US,AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 256, no. 8, 25 April 1984 (1984-04-25), pages 5132-5136, XP002030852 the whole document -----	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9814473 A	09-04-1998	PL 316416 A	14-04-1998
		AU 4565197 A	24-04-1998
		BR 9712259 A	25-01-2000
		CN 1238782 A	15-12-1999
		EP 0932623 A	04-08-1999
		GB 2333453 A	28-07-1999
		HU 9904368 A	28-06-2000
		PL 332632 A	27-09-1999
JP 6128287 A	10-05-1994	NONE	
JP 6041191 A	15-02-1994	NONE	
WO 9724371 A	10-07-1997	IT RM950850 A	27-06-1997
		AU 720411 B	01-06-2000
		AU 1306697 A	28-07-1997
		BR 9612346 A	28-12-1999
		CA 2241171 A	10-07-1997
		EP 0871662 A	21-10-1998
		NO 982777 A	16-06-1998
JP 8269090 A	15-10-1996	NONE	
EP 0583074 A	16-02-1994	JP 2782142 B	30-07-1998
		JP 6040944 A	15-02-1994
		CN 1090201 A,B	03-08-1994
		DE 69326513 D	28-10-1999
		DE 69326513 T	13-04-2000
		US 5449661 A	12-09-1995
JP 2062828 A	02-03-1990	NONE	

PATENT COOPERATION TREATY

REC'D 26 SEP 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PAC/19599		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02128	02/06/2000	02/06/1999
International Patent Classification (IPC) or national classification and IPC C07K7/00		
Applicant REGEN THERAPEUTICS PLC		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/12/2000	26.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715

Form PCT/IPEA/409 (cover sheet) (January 1994)

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-40 as originally filed

Claims, No.:

1-35 as originally filed

Drawings, sheets:

1-18 as originally filed

Sequence listing part of the description, pages:

25-40, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 21 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 21 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☒ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1,3-5,7-32(all partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,3-5,7-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,3-5,7-32
Industrial applicability (IA)	Yes:	Claims	1,3-5,7-20,22-32
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

In response to the invitation to pay additional fees the applicant has chosen not to pay any additional fee and to restrict the examination to the subject-matter of subject 4, that is: peptides having the structure defined by one of the SEQ ID Nos 19-32, peptides containing them, their compositions and use and antibodies to said peptides (claims 1,3-5,7-32 all partially).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:WO-A-9814473
D2:FEBS LETTERS Vol.229, No.2, 1988, 265-272
D3:Gene, Vol.154(1995),259-263
D4:JP06041191 & DERWENT AN=1994-089332
D5:EP-A-0583074
D6:Michwissnschaft, Vol.43, No.11, 1988, 705-707

I.NOVELTY

Partly due to the language used ("including", "substantially") the claims 1,3-5,7 and the

related claims 9-32 are considered to lack novelty under Art.33(2) PCT for the following reasons:

1)Due to their wording ("includes") the claims 1,4 and 5 include colostrinin itself. D1 discloses colostrinin and its use in the treatment of chronic disorders of the central nervous system and the immune system. Hence said claims 1,4 and 5 and the related claims 9-30 are considered to lack novelty under Art.33(2) PCT.

2)D2 discloses the structure of bovine [SAC]-casein (Fig.3). Hence the claims 1,4 and 5 lack novelty.

3)The same reasoning applies, mutatis mutandis, in view of D3 (see Fig.1) disclosing the sequence of ovine β-casein, rendering not novel the claims 1,4 and 5.

4)Document D4 discloses fragments of β-casein for medical purposes comprising several of the present compounds (see table page 6). In view of this disclosure the claims 1,3-5,7 and the related claims 9-18,21-30 are considered to lack novelty under Art.33(2) PCT.

5)D5 discloses a peptide that substantially consists of SEQ ID No 21 (e.g., see Table 2) and its medical use, rendering the claims 1,3-5,7 and the claims 9-18,21-30 not novel.

6)D6 describes fragments of bovine β-casein in the region corresponding to the SEQ ID Nos 23 and 24 of the application and antibodies to said peptides, taking away the novelty of the claims 1,3-5,7,31 and 32.

II.INVENTIVE STEP

1)The closest prior art is considered to be a multitude of documents all relating to disclosing colostrinin and/or β-casein and fragments thereof and their use, e.g. in the treatment of chronic disorders of the central nervous system and the immune system (e.g., see D1-D6).

2)The novel subject-matter relates to the specific fragments having SEQ ID No 19-32 of colostrinin/β-casein. Said compounds can be used for the same purpose.

3)The problem to be solved may therefore be considered to be the provision of alternative peptides of colostrinin/β-casein to be used in the treatment of the same diseases, e.g., chronic disorders of the central nervous system and the immune system.

4)Due to the high, in many cases even complete overlap of the present compounds and the prior art compounds it is considered that an expert would expect many of said compounds to have an activity similar to the prior art compounds. Therefore, in order to acknowledge an inventive step to the novel compounds of the present application, they

should have been demonstrated to exhibit unexpected advantageous properties, which however are lacking. Hence said novel subject-matter is considered to lack an inventive step under Art.33(3) PCT.

For the assessment of the present claims 9-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1)The use of the vague expression "substantially" renders the scope of the claims 1,3,5,7 unclear under Art.6 PCT.

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(54) Title: PEPTIDES

(57) Abstract: The amino acid sequence of several peptides present in Colostrinin is disclosed. These peptides are useful, inter alia, in the treatment of disorders of the immune system and the central nervous system.

PEPTIDES

The present invention relates to peptides. More particularly the invention relates to certain peptides isolated from Colostrinin. The invention also relates to therapeutic uses of the peptides and to antibodies derived therefrom.

Colostrum is the thick, yellowish fluid produced by a mammalian mother's breasts during the first few days after childbirth. It is the first lacteal secretion post parturition and it contains a high concentration of immunoglobulins (IgG, IgM and IgA) and other proteins. It is replaced by mature breast milk about four to five days after birth. Compared with mature breast milk, colostrum contains low sugar and iron, but is rich in lipids, proteins, mineral salts, vitamins and immunoglobulins. Colostrum also contains various floating cells such as granular and stromal cells, neutrophils, monocyte/macrophages and lymphocytes and includes growth factors, hormones, cytokines and polypeptide complexes.

Various factors have been isolated and characterised from mammalian colostrum. In 1974, Janusz et al (FEBS Lett., 49, 276-279) isolated a proline-rich polypeptide (PRP) from ovine colostrum. It has since been discovered that mammals other than sheep have analogues of PRP as a component of their colostrum. PRP has since been called Colostrinin (and is sometimes called Colostrinine).

M. Janusz & J. Lisowski in "Proline-Rich Polypeptide (PRP) - an Immunomodulatory Peptide from Ovine Colostrum" (Archivum Immunologiae et Therapiae Experimentalis, 1993, 41, 275-279) mentioned that PRP from ovine colostrum has immunotropic activity in mice.

A. Dubowska-Inglot et al in "Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes" (Archivum Immunologiae et Therapiae Experimentalis, 1996, 44, 215-224) discussed the use of Colostrinin in the treatment of Alzheimer's disease. The use of Colostrinin in the treatment of Alzheimer's disease, and other conditions, was also discussed in WO-A-98/14473 and in "Colostrinin: a Proline-Rich Polypeptide (PRP) Complex Isolated from Ovine Colostrum for Treatment of Alzheimer's Disease. A Double-Blind, Placebo-Controlled Study", Leszek,J. et al, Archivum Immunologiae et Therapiae Experimentalis, 1999, 47, 377-

385.

Colostrinin, in its natural form, is obtained from mammalian colostrum. As described in WO-A-98/14473, analysis by electrophoresis and chromatography has shown that Colostrinin has the following properties:

(i) it has a molecular weight in the range 16,000 to 26,000 Daltons (this was shown by electrophoresis in the presence of SDS);

(ii) it is a dimer or trimer of sub-units each sub-unit having a molecular weight in the range 5,000 to 10,000 Daltons (this was shown by acrylamide gel electrophoresis in the presence of SDS);

(iii) it contains proline, and the amount of proline is greater than the amount of any other single amino acid (this can be shown by conventional amino acid analysis).

By means of these techniques it was shown that ovine Colostrinin has a molecular weight of about 18,000 Daltons, is made up of three non-covalently linked sub-units each having a molecular weight of about 6,000 Daltons and includes about 22 wt% proline. The amino-acid composition of ovine Colostrinin was shown to be made up of the following number of residues per sub-unit: lysine - 2, histidine - 1, arginine - 0, aspartic acid - 2, threonine - 4, serine - 3, glutamic acid - 6, proline - 11, glycine - 2, alanine - 0, valine - 5, methionine - 2, isoleucine - 2, leucine - 6, tyrosine - 1, phenylalanine - 3 and cysteine - 0.

We have now further analysed the composition of Colostrinin in order to try to identify its components, so that a synthetic form of Colostrinin can be produced.

We have concluded that Colostrinin contains peptide fragments from at least two different proteins: annexin; and β-casein. In addition, Colostrinin contains a number of other peptide fragments which do not have any known precursor protein; these amino acid sequences may be derived from an unknown precursor protein, or they may have no precursor protein. It is believed that some of the peptide sequences are from a β-casein homologue.

According to one aspect of the present invention there is provided a peptide having one of the following amino acid sequences A-1 to D-1:

Group A: Peptides of unknown precursor

A-1	LQTPQPLLQVMMEPQGD	
A-2	MPQNFYKLPQM	
A-3	VLEMKFPPPPQETVT	
A-4	LKPFPKLKVEVFPFP	
A-5	SEQP	
A-6	DKE	
A-7	DPPPPQS	
A-8	LNF	

Group B: Peptides (possibly) having β-casein homologue precursor

B-1	VLPPNVG	
B-2	KYKLQPE	
B-3	SEEMP	
B-4	DSQPPV	
B-5	FPPPK	
B-6	VVMEV	
B-7	DLEMPVLPVEPFPFV	
B-8	LFFFLPVVNVLP	
B-9	MQPPPLP	
B-10	DQPPDVEKPDLQPFQVQS	

Group C: Peptides having β-casein precursor

C-1	VYPFTGPIPN	(Casein Position 74-83)
C-2	SLPQNILPL	(Casein Position 84-92)
C-3	TQTPVVVPPF	(Casein Position 93-102)
C-4	LQPEIMGVPKVKETMVPK	(Casein Position 103-120)
C-5	HKEMPFPKYPVEPFTESQ	(Casein Position 121-138)
C-6	SLTLTDVEKLHLPLPLVQ	(Casein Position 139-156)
C-7	SWMHQPP	(Casein Position 157-163)
C-8	QPLPPTVMFP	(Casein Position 164-173)
C-9	MHQPPQPLPPTVMFP	(casein Position 159-173)
C-10	PQSVLS	(Casein Position 174-179)

C-11 LSQPKVLPVPQKAVPQRDMPIQ (Casein Position 180-201)

C-12 AFLLYQE (Casein Position 202-208)

C-13 FLLYQEPVLGPVR (Casein Position 203-214)

C-14 RGPFPILV (Casein Position 214-222)

Group D: Peptides having annexin precursor

D-1 ATFNRYQDDHGEEILKSL (Annexin Position 203-220)

It is possible that the peptides in group A are also derived from the β-casein homologue, but there is currently no evidence to support this conclusion.

These peptides may be provided in substantially isolated form. Furthermore, a composition may be provided which contains two or more of the above peptides, in combination.

In respect of the peptides A-1 to B-10, the invention further includes any peptide which includes the specified amino acid sequence. In respect of the peptides A1 to D1, the invention further comprises any peptide which includes an amino-terminal amino acid sequence corresponding to the specified sequence. Thus, with reference to peptide A-1, for example, the invention encompasses any peptide having the N-terminal amino acid sequence LQTPQPLLQVMMEPQGD; the same applies to peptides A-2 to D-1. For the avoidance of doubt, it is stated that the amino-terminal end is on the left hand side of the sequence, in accordance with the usual convention. It will be appreciated that any of the specified amino acid sequences may be provided with an inert amino acid sequence on the amino-terminal and/or the carboxy-terminal end thereof. The invention further includes physiologically acceptable active derivatives of the peptides.

The peptides can be obtained by a number of techniques. In one embodiment, they can be prepared naturally by isolation from Colostrinin or colostrum. In a preferred embodiment, they are prepared by a conventional technique for peptide synthesis, such as by solid-phase or liquid-phase peptide synthesis. Alternatively, the gene sequence encoding the peptides can be constructed by known techniques such as expression vectors or plasmids and transfected into suitable microorganisms that will express the DNA sequences, whereby the peptides can be later extracted from the medium in which the microorganisms are grown. Thus, the invention also embraces a DNA sequence

encoding the peptides described above, and a recombinant vector prepared by inserting said DNA in a vector.

The peptides, either alone or in combination with one another, have a number of therapeutic uses.

In one advantageous embodiment, one or more of peptides A-1 to D-1 may be used in the treatment of disorders of the central nervous system, particularly chronic disorders of the central nervous system. The disorders of the central nervous system that may be treated include neurological disorders and mental disorders. Examples of neurological disorders that may, with advantage, be treated include dementia, and also disorders that cause dementia, such as neurodegenerative disorders. Neurodegenerative disorders include, for example, senile dementia and motor neurone disease; Parkinson's disease is an example of a motor neurone disease that can be treated. Alzheimer's disease is an example of a neurodegenerative disease that can be treated. Examples of mental disorders that can be treated by one or more of the peptides include psychosis and neurosis. For example, the peptides may be used to treat emotional disturbances, especially the emotional disturbances of psychiatric patients in a state of depression. The peptides may also be used as an auxiliary withdrawal treatment for drug addicts, after a period of detoxification, and in persons dependent on stimulants.

In another advantageous embodiment of the invention, one or more of peptides A-1 to D-1 may be used in the treatment of disorders of the immune system, particularly chronic disorders of the immune system the may occur spontaneously in people of advanced age. The peptides can also be used in the treatment of diseases requiring immuno-modulation. The peptides are useful in the treatment of a variety of diseases with an immunological and infectious basis. For example, they can be used to treat chronic diseases with a bacterial and viral aetiology, and to treat acquired immunological deficiencies that have developed, for example, after chemotherapy or radiotherapy of neoplasms. The peptides may be used for treating chronic bacterial and viral infections requiring non-specific immunostimulation and immunocorrection.

A chronic disorder is a disorder that has persisted, or is expected to persist, for a long time, i.e., at least 3 months and usually at least 6 months.

One or more of the peptides may be used for improving the development of the immune system of a new born child. It is a further feature of the invention to use the peptides to correct immunological deficiencies in a child. These uses of the peptides may be particularly applicable to babies or children who have been deprived of colostrum. This may occur, for example, in babies and children who were not breast fed from birth.

The peptides, either alone or in combination with one another, also have diagnostic and research applications. For example, the synthetic peptides, as well as the corresponding antibodies described below, may be used to recognise pathological processes occurring in a host. These processes may be induced by excessive production or inhibition of the peptides or the antibodies. Once the pathological process associated with a particular level of the peptides or the antibodies is known, measuring the production of the peptides and the antibodies in body fluids may be used to determine pathological processes taking place in the host.

According to another aspect of the invention, we provide the use of one or more of peptides A-1 to D-1 as a dietary supplement. This dietary supplement is particularly useful for babies, especially premature babies and babies at term, and for young children to correct deficiencies in the development of their immune system. The dietary supplement may also be used as a dietary supplement for adults, including senile persons, who have been subjected to chemotherapy, or have suffered from cahexia, or weight loss due to chronic disease.

In an aspect of the invention, we provide a dietary supplement comprising an orally ingestible combination of one or more of peptides A-1 to D-1 in combination with a physiologically acceptable carrier. The dietary supplement may be provided in liquid or solid form; the dietary supplement may suitably be provided in the form of a tablet. The dietary supplement may be provided in the form of a baby food formula. The dietary supplement may include, as an additive, lactoferrin and/or selenium and/or a group of cytokines containing members of the interferon family.

In accordance with the invention, one or more of peptides A-1 to D-1 may be administered prophylactically in order to help to prevent the development of disorders of the central nervous system and the immune system.

The peptides according to the invention may be used to promote the dissolution of β-amyloid plaques, and, therefore, the peptides may be used in the treatment of any disease which is characterised by the development of β-amyloid plaques.

The peptides according to the invention may be administered in a dosage in the range 1 ng to 10 mg. A dosage unit of about 3 μg is typical. However, the optimum dosage will, of course, depend upon the condition being treated.

The peptides according to the invention may be formulated for administration in any suitable form. Thus, the invention further provides a composition, especially a pharmaceutical composition, which includes one or more of the peptides in combination with a physiologically acceptable carrier. The peptides may, for example, be formulated for oral, topical, rectal or parenteral administration. More specifically, the peptides may be formulated for administration by injection, or, preferably, in a form suitable for absorption through the mucosa of the oral/nasopharyngeal cavity, the alimentary canal or any other mucosal surface. The peptides may be formulated for administration intravenously, subcutaneously, or intramuscularly. The oral formulations may be provided in a form for swallowing or, preferably, in a form for dissolving in the saliva, whereby the formulation can be absorbed in the mucous membranes of the oral/nasopharyngeal cavity. The oral formulations may be in the form of a tablet for oral administration, lozenges (i.e. a sweet-like tablet in a form suitable to be retained in the mouth and sucked), or adhesive gels for rubbing into the gum. The peptides may be formulated as an adhesive plaster or patch, which may be applied to the gums. The peptides may also be formulated for application to mucous-membranes of the genito-urinary organs. The topical formulations may be provided in the form of, for example, a cream or a gel.

One or more of the peptides may be incorporated into products like milk or cheese spread.

According to another aspect of the invention there is provided a pharmaceutical composition comprising a peptide containing the amino acid chain LQTPQPLLQVMMEPQGD; DPPPPQS; and/or LFFFLPVVNVLP or use as an immunosuppressant, for use in the treatment of autoimmune disorder, and/or for use in suppressing the rejection of transplanting organs. The invention also embraces the

use of one or more of these peptides in the manufacture of a medicament for use as an immunosuppressant, for use in the treatment of autoimmune disorder, and/or for use in suppressing the rejection of transplanting organs.

We have found that the ratio of the peptides in colostrum varies over time. Owing to hormonal changes, many proteins secreted into colostrum become sequentially degraded. The longer the time from parturition the more extensive the degradation can be. This knowledge will help with the design of new baby food formulas as well as many drugs for immuno-compromised patients.

In another aspect, the invention provides an antibody for each of the peptides A-1 to D-1, and provides compositions containing said antibodies. In particular the invention provides the antibodies in substantially isolated form. The antibodies can be produced by injecting a suitable mammalian subject, such as a rabbit, with the corresponding peptide (with a suitable adjuvant), then recovering the antibodies from the subject after allowing time for them to be produced. This technique is described in detail in Example 3. It is possible to test that the correct antibody has been produced by ELISA (enzyme-linked immunosorbent assay) using the synthetic peptides as antigens. The antibodies can be further tested against the natural peptides in Colostrinin as confirmation that the synthetic peptides do correspond to the natural peptides found in Colostrinin. The antibodies have potential uses in therapy, as a diagnostic tool and as a research tool.

The invention also encompasses the selective administration of one or more of peptides A-1 to D-1, at selected times to a patient, and the selective administration of one or more of the antibodies for the peptides in order to switch on or off the activity of the peptides at a selected time.

A selection of selected ones of the peptides and/or antibodies may be provided in a single composition which is specially tailored to produce a particular effect. For example, for a person with an immunological disorder, the composition can be specially tailored for that disorder. The composition may be specially selected for more than one disorder. The composition may be specially selected to restore or produce a particular balance in a subject.

In some applications it may be desirable to provide a pharmaceutical

composition which contains one or more of the peptides and one or more of the antibodies in combination with a physiologically acceptable carrier.

The invention further embraces the use of one or more of the peptides and/or antibodies in the manufacture of a medicament for use in any of the therapeutic applications described above.

Reference is now made to the accompanying drawing in which Figs. 1 to 18 are Matrix-Assisted Laser Desorption Time-of-Flight Mass Spectroscopy (LDMS) spectra of certain peptides according to the invention.

The invention will now be further described with reference to the following examples.

Example 1

Preparation of Colostrinin

Colostrinin can be prepared by techniques already disclosed in the prior art, including, for example, WO-A-98/14473. Colostrum collected from the ewe within 12 hours post parturition can be purified by centrifuging to eliminate cellular and lipidic components, pH shifting to eliminate nutritional components, ammonium sulfate precipitation, ion exchange chromatography and molecular sieving.

Example 2

Identification of the Components of Colostrinin

Initially the Colostrinin produced according to example 1 was analysed by SDSPAGE, by means of which we found the following two peptides: VLEMKFPPPPQETVT (A-3) and LKPFKLKVEVFPEP (A-4). However, we could not identify any other peptides with this technique, so we turned to hplc.

The Colostrinin produced in example 1 was fractionated by hplc using a C-18 reverse-phase column. This technique was used to separate the peptides exhibiting different hydrophobic patterns, present in Colostrinin. The hplc column was obtained from Separation Methods Technologies (who are based in Newark, Delaware, U.S.A). The column type was designated C-18 and was 150 mm in length by 10 mm in diameter. The column was packed with particles having a particle size of 3 μm having

a pore size of 30 nm. The pump module and diode array were supplied by Beckman (who are based in Fullerton, California, U.S.A.): a Beckman System Gold 126 pump module was used, and a Beckman System Gold 168 diode array detector module was used.

The Colostrinin was loaded in 0.1% trifluoroacetic acid (TFA) dissolved in hplc grade water. A 500 µl sample, containing approximately 900 picomole of the Colostrinin was loaded on the column, the column having been equilibrated prior to loading. After approximately 10 minutes of intensive washing, the material was eluted by gradient formed from solutions A and B, under a regime indicated in Table 1. During this time, the flowrate through the column was 0.06 ml/min.

Table 1

Time/Min	% Solvent A	% Solvent B
0.00	95.0	5.0
10.00	30.0	70.0
100.00	0.0	100.0
140.00	95.0	5.0
150.00	95.9	5.0

Solvent A: 0.1% TFA (trifluoroacetic acid) in hplc grade water.

Solvent B: 70% acetonitrile fluoride and 0.09% TFA in hplc grade water.

The peptides found at the peaks in the hplc were then individually analysed using Edman Degradation; this was done using a Beckman LF3000 sequencer. Each concentrated fraction was loaded into a pre-salted Beckman peptide support disk. The samples were sequenced using the standard Edman degradation steps. Typically, 10 to 100 pmoles were used to generate 10 to 25 cycles for each analysis.

Subsequently, each fraction was analysed by the Inline hplc System. This used a Hewlett Packard PTH-AA column having a length of 250 mm and a diameter of 2.1 mm. The Beckman System Gold 126 pump module was used, and the Beckman System Gold 168 diode array detector module was used. The flowrate in the column was 0.275

ml/min, and the solvent composition was varied as shown in Table 2.

Table 2

Time/Min	% Solvent A	% Solvent B
0.00	80.0	20.0
0.10	62.0	38.0
17.10	10.0	90.0
28.10	87.5	12.5

Solvent A: 3.5% THF (tetrahydrofuran), 1.5% acetonitrile fluoride premix, 1% acetic acid & 0.02% TEA (triethanolamine) in hlpc grade water.

Solvent B: 12% isopropanol in acetonitrite.

The structure of the peptides A-1 to D-1 was then used for comparative studies with sequences registered in two known computer programs: Wu-Blast 2 of the National Center for Biotechnology Information NR Protein Data Base; and Beauty - Post Processing provided by the Human Genome Center, Baylor College of Medicine, Houston, Texas, USA. This made is possible to determine whether any of the peptide sequences P1-P32 were already known.

The results of the Edman degradation are summarised in Table 3. The subsequent analysis with the computer programs revealed that there were at least two different precursor proteins for the peptides in Colostrinin: β-casein and annexin. Furthermore, by using the Tremble program, it was possible to find evidence that some of the peptides may have a precursor which is a casein homologue. Finally, some of the peptides had unique sequences with no homology to any known protein.

Table 3

Peak No.	Elution time min.	Area %	AA sequence		
			Casein homologue	Unknown precursor	Casein/Annexin precursor
1	8.54	1.181	VVMEV (B-6)		ATFNRYQDDHGEEILKSL (D-1)

2	29.086	0.124		SEQP (A-5)	
3	53.775	0.579			
4	56.815	0.111	FPPPK (B-5)		LSQPKVLPVPQKAPQPRDM PIQ (C-11)
5	58.044	2.101	DSQPPV (B-4)		LSQPKVLPVPQKAPQPRDM PIQ (C-11)
6	60.488	0.588	MQPPPLP (B-9)		LSQPKVLPVPQKAPQPRDM PIQ (C-11)
7	62.684	1.273		DPPPPQS (A-7)	
8	65.44	3.247		LQTPQPLLQV MMEPQGD (A-1)	LSQPKVLPVPQKAPQPRDM PIQ (C-11)
9	66.775	0.683	DQPPDVEKPDLQ PFQVQS (B-10)		LSQPKVLPVPQKAPQPRDM PIQ (C-11)
10	67.929	2.943	LFFFLPVVNVLP (B-8)		LSQPKVLPVPQKAPQPRDM PIQ (C-11) MHQPPQPLPPTVMFP (C-9)
11	69.229	2.717	SEEMP (B-3)		LSQPKVLPVPQKAPQPRDM PIQ (C-11) HKEMPFPKYPVEPFTESQ (C-5)
12	70.984	2.964	KYKLQPE (B-2)		LSQPKVLPVPQKAPQPRDM PIQ (C-11) HKEMPFPKYPVEPFTESQ (C-5)
13	72.547	1.423	VLPPNVG (B-1)		LSQPKVLPVPQKAPQPRDM PIQ (C-11)
14	74.09	1.425	DLEMPVLPVEPF PFV (B-7)		SLPQNILPL (C-2)
15	76.558	5.268		MPQNFYKLP QM (A-2)	MHQPPQPLPPTVMFP (C-9
16	78.506	6.978		LNF (A-8)	MHQPPQPLPPTVMFP (C-9)

17	80.94	4.224			MHQPPQPLPPTVMFP (C-9) SLTLTDVEKLHLPLPLVQ (C-6) PQSVLS (C-9)
18	83.8	1.025			ND
19	84.314	2.151			MHQPPQPLPPTVMFP (C-9)
20	85.707	3.103			SWMHQPP (C7)
21	87.061	1.047			ND
22	87.907	1.529			ND
23	88.921	1.311			MHQPPQPLPPTVMFP (C-9) SLTLTDVEKLHLPLPLVQ (C-6) TQTPVVVPPF (C-3) VYPFTGPIPN (C-1)
24	89.856	1.114			ND
25	91.343	0.906			ND
26	92.667	0.821			ND
27	93.521	3.893			ND
28	94.751	1.426			ND
29	95.82	0.272			HKEMPFPKYPVEPFTESQ (C-5)
30	96.697	3.164			QPLPPTVMFP (C-8) HKEMPFPKYPVEPFTESQ (C-5)
31	97.938	3.266			ND
32	99.893	5.621			HKEMPFPKYPVEPFTESQ (C-5)
33	100.9	5.032			ND
34	102.709	4.007			AFLLYQE (C-12) HKEMPFPKYPVEPFTESQ (C-5)
35	104.74	3.275			ND

36	106.01	2.231			ND
37	170.75	3.037			ND
38	108.782	2.173			SLTLTDVEKLHLPLPLVQ (C-6) HKEMPFPKYPVEPFTESQ (C-5) SLPQNILPL (C-2) VYPFTGPIPN (C-1)
39	111.056	5.375			HKEMPFPKYPVEPFTESQ (C-5)
40	112.679	1.901			ND
41	114.707	0.436			ND
42	8.54	1.181			ATFNRYQDDHGEEILKSL (D-1)

ND indicates that these fractions were not analysed.

DKE (A-6), LQPEIMGVPKVKETMVPK (C-4), FLLYQEPVLGPVR (C-11) and RGPFPILV (C-13) were also detected by hplc, although their presence is not indicated in the above table.

Example 3

Production of the Antibodies

The peptides identified in example 2 were produced by the synthetic technique known as the solid phase method. This method involved the following steps:

1. Wash pre-loaded resin with DMF (dimethylformamide), then drain completely.
2. Add 10 ml of 20% piperidine/DMF to resin. Shake for 5 mins, then drain.
3. Add another 10 ml of 20% piperidine/DMF. Shake for 30 mins.
4. Drain reaction vessel and wash resin with DMF four times. Then wash once with DCM (dichloromethanol). Check beads using the ninhydrin test - the beads should be blue.
5. The coupling step was carried out as follows:

Prepare the following solution:

1 mmole Fmoc (i.e. fluorenylmethyloxycarbonyl) amino acid

2.1 ml of 0.45 M HBTU/HOBT (1 mmol) (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/N-hydroxybenzotriazole-H_2O)

348 µl of DIEA (2 mmol) (diisopropylethylamine)

Add the solution to the resin and shake for a minimum of 30 minutes.

6. Drain reaction vessel and wash the resin again with DMF four times and with DCM once.

7. Perform the ninhydrin test:

If positive (no colour) - proceed to step 2 and continue synthesis.

If negative (blue colour) - return to step 5 and recouple the same Fmoc amino acid.

8. After the synthesis was complete, the peptide was cleaved from the resin with 5% H_2O, 5% phenol, 3% Thionisole, 3% EDT (ethanedithiol), 3% triisopropylsilane and 81% TFA for 2 hours.

9. After 2 hours, filter into cold MTBE (methyl t-butyl ether). The precipitated peptide was then washed twice with cold MTBE and dried under nitrogen gas.

10. The molecular weight of the synthesised peptides was checked by Matrix-Assisted Laser Desorption Time-of-Flight Mass Spectroscopy (LDMS), and the purity was checked by hplc using a C-18, 300 Angstrom, 5 µm column. The resulting spectra of some peptides are shown in Figs. 1 to 18.

To each N-terminal end of the synthetic peptides, L-cysteine was attached, and the peptide was formed into a ring so that the cysteine group lay between the N-terminal and the C-terminal ends of the synthetic peptide. This facilitated peptide conjugation with Keyhole Hemolymph (KHL). The shorter peptides (i.e. those containing 9 or fewer amino acids) were artificially elongated with biologically inert amino acids prior to attaching the L-cysteine. This was done in order to facilitate annealing and increase the antigenicity of the shorter peptides.

Table 4 shows a number of the peptides that were formed and indicates the figure

number of the drawings which illustrates the laser desorption mass spectrum.

Table 4

PEPTIDE SYNTHESISED	ORIGINAL PEPTIDE	FIGURE NO.
NH_2-(Ac)CLQTPQPLLQVMMEPQGD-OH	A-1	1
NH_2-(Ac)CMPQNFYKLPQM-OH	A-2	2
NH_2-(Ac)CVLEMKFPPPPQETVT-OH	A-3	3
NH_2-(Ac)CLKPFPKLKVEVFPFP-OH	A-4	4
NH_2-SEQPGGGC-OH	A-5	5
NH_2-(Ac)CGVLPPNVG-OH	B-1	6
NH_2-(Ac)CGGGKYKLQE-OH	B-2	7
NH_2-(Ac)CGGGSEEMP(amide)-OH	B-3	8
NH_2-(Ac)CGGGDSQPPV-OH	B-4	9
NH_2-CFPPPKGGGC-OH	B-5	10
NH_2-(Ac)CGGGVVMEV-OH	B-6	11
NH_2-(Ac)CDLEMPVLPVEPFPFV-OH	B-7	12
NH_2-(Ac)CLFFFLPVVNVLPI-OH	B-8	13
NH_2-(Ac)CMQPPPLP-OH	B-9	14
NH_2-(Ac)CDQPPDVEKPDLQPFQVQS-OH	B-10	15
NH_2-(Ac)CGAFLLYQE-OH	C-12	16
NH_2-(Ac)CATFNRYQDDHGEEILKSL-OH	D-1	17
NH_2-DPPPQSGGGC-OH	A-7	18

The invention further provides each of the peptides specified in Table 4, and the cyclisised version of each of these peptides, especially in isolated form and produced by a synthetic process. The term "Ac" represents an acyl group.

For immunisation, two young adult rabbits (5-6 months old, weighing 5-6 lbs [2.3-2.7kg]) were used. Each antigen (i.e., each synthetic peptide) was given subcutaneously and intramuscularly in 0.1 ml injections at ten different sites. The protocol used followed

the following sequence:

Day	Procedure
0	Prebleed & initial inoculation of rabbit with 200 µg of the peptide at 0.5 ml of conjugate solution mixed with an equal volume of complete Freund's adjuvant (mineral oil/emulsifier/killed mycobacteria).
14	Boost inoculation with 200 µg of the peptide at 0.5 ml of conjugate solution mixed with an equal volume of incomplete Freund's adjuvant (mineral oil/emulsifier).
28	Boost (as on day 14) Production Bleed (approx. 20ml sera)
42	Boost (as on day 14) Production Bleed (approx. 20ml sera)
56	Boost (as on day 14) Production Bleed (approx. 20ml sera)
70	Boost (as on day 14) Production Bleed (approx. 20ml sera)

This protocol may be varied. For example, the frequency of the production bleed depends upon, inter alia, the size and health of the host species.

The sera produced by this protocol were used for IgG purification on a Protein A matrix (from Sigma, based in St. Louis, MO, USA). The protocol was as follows:

1. Wash columns with 10 ml 1 X PBS (phosphate buffered saline). There were two 1 m column arranged in tandem each containing the Protein A matrix.
2. Add 3 ml of the serum to 3 ml of PBS and divide this mixture between the two columns.
3. Collect the serum into a test tube as it drains through the column.
4. When the serum finishes draining, pour the washed serum back into the column and begin collecting flow through again. Repeat this step 5 to 6

times.

5. Wash the columns with 10 ml of 1 X PBS.
6. Prepare several 1 ml tubes with 50 µl of 1 M TRIS (2-amino-2-hydroxymethyl-1,3-propanediol) (pH = 9,5).
7. Add 1 ml of elution buffer (100 mM glycine, pH = 2.8) to each tube and collect 1 ml of flow therethrough.
8. Move to the next prepare tube and repeat step 7.
9. Test each 1 ml sample by preparing ELISA plate with 10 µl of Bradford Assay and add 50µl of each 1 ml flow through. Keep the samples that change the Bradford Assay from red to blue.
10. Dialyse the positive 1 ml samples together in 4 litres of 1X PBS at pH = 7.2 for at least 24 hours.
11. Use spectrometer at 280 nm to find concentration of IgG in solution (extinction coefficient = 1.4).
12. To store IgG solution, keep frozen at -4°C to -20°C.

Table 5 shows the results for certain antibodies.

Table 5

Peptide used to produce Antibody	Serum used (ml)	Purified Ab volume (ml)	OD_{280}	IgG (mg/ml)	Total IgG (mg)
A-1	10	15	3.80	2.71	40.71
A-2	10	15	2.13	1.52	22.82
A-3	10	15	2.93	2.09	31.39
A-4	10	15	3.57	2.55	38.25
A-5	6	12	3.02	2.16	25.88
B-1	10	15	2.64	1.89	28.28
B-2	6	13	4.94	3.53	45.87
B-3	6	13	5.01	3.58	46.52

Peptide used to produce Antibody	Serum used (ml)	Purified Ab volume (ml)	OD_{280}	IgG (mg/ml)	Total IgG (mg)
B-4	10	15	2.68	1.91	28.71
B-5	10	15	2.28	1.63	24.43
B-6	10	15	2.50	1.79	26.78
B-7	10	15	2.90	2.07	31.07
B-8	10	15	3.40	2.43	36.43
B-9	10	15	3.80	2.71	40.71
B-10	10	15	4.18	2.99	44.79
C-12	10	15	1.95	1.39	20.89
D-1	10	15	2.32	1.66	24.86
A-7	6	12	3.33	2.38	28.54

The level of antibodies in the serum was established by ELISA (enzyme-linked immunosorbent assay) with the corresponding synthetic peptide antigen. This technique involved the following steps:

1. The antigen was diluted with a 0.1 M bicarbonate buffer (pH 9.0) to yield a 10 µg of antigen/ml solution. A volume of 50 µl of this solution was placed into each microwell of a 96 well plate.
2. The plates were covered and incubated at 37°C for 3 hours.
3. The wells were washed with a coupling buffer and blocked using 200 µl of Pierce standard solution of BSA (bovine serum albumin).
4. 50 µl of dilutent BSA (0.75% soln.) was pipetted into each well. 50 µl of antibody serum sample diluted 1:100 in dilutent BSA were placed in lane A of each row.
5. 1:2 serial dilutions were performed moving down the plate.
6. The plates were covered and incubated at room temperature for 60 minutes.
7. The plates were washed four times with PBS wash solution.
8. A volume of 50 µl of goat anti-rabbit IgG (H&L) HRP conjugate at 1:1000

dilution in BSA was pipetted into each well and incubated at room temperature for 60 minutes (H&L = heavy and light chain; HRP = horseradish peroxidase).

9. The plates were washed four times with PBS wash solution.

10. A volume of 50 µl of substrate solution 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)-diammonium salt (ABTS available from Pierce, which is used to help visualise the extent of the antibody/antigen reaction) was pipetted into each well and incubated at room temperature for about 2 minutes.

11. The reaction was stopped by adding 50 µl of 1% SDS (sodium dodecyl sulfate) into each well.

12. The wells were then read on a dynoplate reader at 405.

The data presented in Table 6 show the serum antibody titers against specific antibodies after the 10 week immunisation protocol.

Table 6

No	Sequences	Titre: (Serum Dilution) Pre Immunization		Post Immunization	
A. Peptides of unknown origin		**R1**	**R2**	**R1**	**R2**
1	LQTPQPLLQVMMEPQGD	0	0	6400	0
2	MPQNFYKLPQM	0	0	6400	25600
3	VLEMKFPPPPQETVT	0	0	6400	12800
4	LKPFPKLKVEVFPFP	0	0	6400	25600
5	SEQP	0	0	3200	25600
6	DKE	ND	ND	ND	ND
7	DPPPPQS	0	0	3400	6200
8	LNF	ND	ND	ND	ND
B. Peptides from casein homologue		**R1**	**R2**	**R1**	**R2**

	1	VLPPNVG	0	0	25600	25600
	2	KYKLQPE	0	0	25600	25600
	3	SEEMP	0	0	25600	12800
	4	DSQPPV	0	0	25600	25600
5	5	FPPPK	0	0	12800	6400
	6	VVMEV	0	0	25600	25600
	7	DLEMPVLPVEPFPFV	0	0	25600	6400
	8	LFFFLPVVNVLP	0	0	200	200
	9	MQPPPLP	0	0	3200	12800
10	10	DQPPDVEKPDLQPFQVQS	0	0	12800	25600
	C. Peptides from β-casein		**R1**	**R2**	**R1**	**R2**
	1	VYPFTGPIPN	ND	0	ND	>10000
	2	SLPQNILPL	ND	0	ND	>10000
	3	TQTPVVVPPF	ND	0	ND	>10000
15	4	LQPEIMGVPKVKEMVPK	ND	0	ND	>10000
	5	HKEMPFPKYPVEPFTESQ	ND	0	ND	>10000
	6	SLTLTDVEKLHLPLPLVQ	ND	0	ND	>10000
	7	SWMHQPP	ND	ND	ND	ND
	8	QPLPPTVMFP	ND	ND	ND	ND
20	9	MHQPPQPLPPTVMFP	ND	0	ND	>10000
	10	PQSVLS	ND	ND	ND	ND
	11	LSQPKVLPVPQKAVPQRDMPIQ	ND	0	ND	>10000
	12	AFLLYQE	ND	0	12800	25600
	13	FLLYQEPVLGPVR	ND	0	ND	>10000
25	14	RGPFPILV	ND	ND	ND	ND
	D. Peptide from annexin		**R1**	**R2**	**R1**	**R2**
	1	ATFNRYQDDHGEEILKSL	0	0	12800	25600

ND = Not Done

In Table 6 the results are shown for two rabbits R1 and R2. In general, these results indicate that the potency of the antibodies produced in respect of peptides was excellent, and therefore that each antibody was the correct antibody for its synthetic peptide antigen. The antibodies produced by this technique were monospecific. However, the antigenic response in respect of peptides A-1, A-7 and B-8 were significantly lower than expected and lead us to predict that these peptides, especially B-8, would be useful as an immunosuppressant, and therefore would be useful in the treatment of autoimmune disorder and in the prevention of organ rejection during, for example, organ transplants.

Example 4

In order to establish that the peptides corresponding to the synthetic peptide antigens exist in Colostrinin we carried out tests to determine whether certain of the antibodies produced a reaction in Colostrinin itself.

We studied the rate at which the peptides A-4, B-7, B-8 and B-9 disappeared from colostrum produced in sheep. The colostrum was collected from the mother's milk at 24 hours, 48 hours and 72 hours post parturition, and the level of the peptides was measured. The peptide level was measured by means of an antigen-antibody reaction, using the antibodies produced by the method of Example 3. The result are shown in Table 7.

Table 7

Peptide:	24 Hour Titre	48 Hour Titre	72 Hour Titre
A-4	12800	6400	3200
B-7	12800	6400	3200
B-8	12800	3200	3200
B-9	12800	12800	3200

These results demonstrated that antibodies had recognised the amino acid

sequences A-4, B-7, B-8 and B-9, and that the concentration of the peptide had diminished over time, owing to binding of the antibody with the peptide.

It will be appreciated that the invention described above may be modified.

CLAIMS:

1. A peptide, in substantially isolated form, which substantially includes the amino-terminal amino acid sequence: LQTPQPLLQVMMEPQGD-OH (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); SEQP (SEQ ID 5); DKE (SEQ ID 6); DPPPPQS (SEQ ID 7); LNF (SEQ ID 8); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); SEEMP (SEQ ID 11); DSQPPV (SEQ ID 12); FPPPK (SEQ ID 13); VVMEV (SEQ ID 14); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS (SEQ ID 18); VYPFTGPIPN (SEQ ID 19); SLPQNILPL (SEQ ID 20); TQTPVVVPPF (SEQ ID 21); LQPEIMGVPKVKETMVPK (SEQ ID 22); HKEMPFPKYPVEPFTESQ (SEQ ID 23); SLTLTDVEKLHLPLPLVQ (SEQ ID 24); SWMHQPP (SEQ ID 25); QPLPPTVMFP (SEQ ID 26); MHQPPQPLPPTVMFP (SEQ ID 27); PQSVLS (SEQ ID 28); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID 29); AFLLYQE (SEQ ID 30); FLLYQEPVLGPVR (SEQ ID 31); RGPFPILV (SEQ ID 32); ATFNRYQDDHGEEILKSL (SEQ ID 33).

2. A peptide, in substantially isolated form, which substantially includes the amino acid sequence: LQTPQPLLQVMMEPQGD (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); DPPPPQS (SEQ ID 7); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); DSQPPV (SEQ ID 12); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS (SEQ ID 18).

3. A peptide, in substantially isolated form, which substantially entirely consists of the amino acid sequence: LQTPQPLLQVMMEPQGD (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); SEQP (SEQ ID 5); DKE (SEQ ID 6); DPPPPQS (SEQ ID 7); LNF (SEQ ID 8); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); SEEMP (SEQ ID 11); DSQPPV (SEQ ID 12); FPPPK (SEQ ID 13); VVMEV (SEQ ID 14); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS

(SEQ ID 18); VYPFTGPIPN (SEQ ID 19); SLPQNILPL (SEQ ID 20); TQTPVVVPPF (SEQ ID 21); LQPEIMGVPKVKETMVPK (SEQ ID 22); HKEMPFPKYPVEPFTESQ (SEQ ID 23); SLTLTDVEKLHLPLPLVQ (SEQ ID 24); SWMHQPP (SEQ ID 25); QPLPPTVMFP (SEQ ID 26); MHQPPQPLPPTVMFP (SEQ ID 27); PQSVLS (SEQ ID 28); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID 29); AFLLYQE (SEQ ID 30); FLLYQEPVLGPVR (SEQ ID 31); RGPFPILV (SEQ ID 32); ATFNRYQDDHGEEILKSL (SEQ ID 33).

4. A peptide according to claim 1, 2 or 3, when obtained by a synthetic process.

5. A peptide obtained by a synthetic process, which substantially includes the amino-terminal amino acid sequence: LQTPQPLLQVMMEPQGD (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); SEQP (SEQ ID 5); DKE (SEQ ID 6); DPPPPQS (SEQ ID 7); LNF (SEQ ID 8); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); SEEMP (SEQ ID 11); DSQPPV (SEQ ID 12); FPPPK (SEQ ID 13); VVMEV (SEQ ID 14); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS (SEQ ID 18); VYPFTGPIPN (SEQ ID 19); SLPQNILPL (SEQ ID 20); TQTPVVVPPF (SEQ ID 21); LQPEIMGVPKVKETMVPK (SEQ ID 22); HKEMPFPKYPVEPFTESQ (SEQ ID 23); SLTLTDVEKLHLPLPLVQ (SEQ ID 24); SWMHQPP (SEQ ID 25); QPLPPTVMFP (SEQ ID 26); MHQPPQPLPPTVMFP (SEQ ID 27); PQSVLS (SEQ ID 28); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID 29); AFLLYQE (SEQ ID 30); FLLYQEPVLGPVR (SEQ ID 31); RGPFPILV (SEQ ID 32); ATFNRYQDDHGEEILKSL (SEQ ID 33).

6. A peptide obtained by a synthetic process, which substantially includes the amino acid sequence: LQTPQPLLQVMMEPQGD (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); DPPPPQS (SEQ ID 7); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); DSQPPV (SEQ ID 12); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS (SEQ ID 18).

7. A peptide obtained by a synthetic process, which substantially entirely consists of the amino acid sequence: LQTPQPLLQVMMEPQGD (SEQ ID 1); MPQNFYKLPQM (SEQ ID 2); VLEMKFPPPPQETVT (SEQ ID 3); LKPFPKLKVEVFPFP (SEQ ID 4); SEQP (SEQ ID 5); DKE (SEQ ID 6); DPPPPQS (SEQ ID 7); LNF (SEQ ID 8); VLPPNVG (SEQ ID 9); KYKLQPE (SEQ ID 10); SEEMP (SEQ ID 11); DSQPPV (SEQ ID 12); FPPPK (SEQ ID 13); VVMEV (SEQ ID 14); DLEMPVLPVEPFPFV (SEQ ID 15); LFFFLPVVNVLP (SEQ ID 16); MQPPPLP (SEQ ID 17); DQPPDVEKPDLQPFQVQS (SEQ ID 18); VYPFTGPIPN (SEQ ID 19); SLPQNILPL (SEQ ID 20); TQTPVVVPPF (SEQ ID 21); LQPEIMGVPKVKETMVPK (SEQ ID 22); HKEMPFPKYPVEPFTESQ (SEQ ID 23); SLTLTDVEKLHLPLPLVQ (SEQ ID 24); SWMHQPP (SEQ ID 25); QPLPPTVMFP (SEQ ID 26); MHQPPQPLPPTVMFP (SEQ ID 27); PQSVLS (SEQ ID 28); LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID 29); AFLLYQE (SEQ ID 30); FLLYQEPVLGPVR (SEQ ID 31); RGPFPILV (SEQ ID 32); ATFNRYQDDHGEEILKSL (SEQ ID 33).

8. A peptide comprising: NH_2-(Ac)CLQTPQPLLQVMMEPQGD-OH (SEQ ID 34); NH_2-(Ac)CMPQNFYKLPQM-OH (SEQ. ID 35); NH_2-(Ac)CVLEMKFPPPPQETVT-OH (SEQ ID 36); NH_2-(Ac)CLKPFPKLKVEVFPFP-OH (SEQ ID 37); NH_2-SEQPGGGC-OH (SEQ ID 38); NH_2-(Ac)CGVLPPNVG-OH (SEQ ID 39); NH_2-(Ac)CGGGKYKLQE-OH (SEQ ID 40); NH_2-(Ac)CGGGSEEMP(amide)-OH (SEQ ID 41); NH_2-(Ac)CGGGDSQPPV-OH (SEQ ID 42); NH_2-CFPPPKGGGC-OH (SEQ ID 43); NH_2-(Ac)CGGGVVMEV-OH (SEQ ID 44); NH_2-(Ac)CDLEMPVLPVEPFPFV-OH (SEQ ID 45); NH_2-(Ac)CLFFFLPVVNVLPI-OH (SEQ ID 46); NH_2-(Ac)CMQPPPLP-OH (SEQ ID 47); NH_2-(Ac)CDQPPDVEKPDLQPFQVQS-OH (SEQ ID 48); NH_2-(Ac)CGAFLLYQE-OH (SEQ ID 49); NH_2-(Ac)CATFNRYQDDHGEEILKSL-OH (SEQ ID 50).

9. A peptide according to any preceding claim, for use as a medicament.

10. A peptide according to claim 9, for use in the treatment of chronic disorders of the central nervous system.

11. A peptide according to claim 10, for use in the treatment of neurological disorders and/or mental disorders.

12. A peptide according to claim 9, for use in the treatment of dementia and/or neurodegenerative diseases.

13. A peptide according to claim 9, for use in the treatment of Alzheimer's disease and/or motor neurone disease.

14. A peptide according to claim 9, for use in the treatment of psychosis and/or neurosis.

15. A peptide according to claim 9, for use in the treatment of chronic disorders of the immune system.

16. A peptide according to claim 9, for use in the treatment of diseases with a bacterial and viral aetiology, and/or for use in the treatment of acquired immunological deficiencies.

17. A peptide according to claim 9, for use in the treatment of chronic bacterial and/or viral infections.

18. A peptide according to claim 9, for use in the treatment of diseases characterised by the presence of β-amyloid plaque.

19. The use of a peptide according to any one of claims 1 to 8, in the manufacture of a medicament for the treatment of chronic disorders of the central nervous system.

20. The use of a peptide according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of chronic disorders of the immune system.

21. A method of treating disorders of the central nervous system and/or of the immune system, comprising administering a therapeutically effective amount of a peptide according to any one of claims 1 to 8 to a patient.

22. A composition comprising a peptide according to any one of claims 1 to 8, in combination with a physiologically acceptable carrier.

23. A composition comprising two or more peptides according to any one of claims 1 to 8, in combination with a physiologically acceptable carrier.

24. A composition according to claim 22 or 23, in a form suitable for injection.

25. A composition according to claim 22 or 23, in a form suitable for absorption through the mucosa of the oral/nasopharyngeal cavity and/or in a form suitable for absorption in the alimentary canal.

26. A composition according to claim 22 or 23, in the form of a tablet, lozenge, gel, patch or plaster.

27. A composition according to claim 22 or 23, in a form suitable for topical application.

28. The use of a peptide according to any one of claims 1 to 8 as a dietary supplement.

29. The use of a peptide according to any one of claims 1 to 8 as a dietary supplement for babies, small children, adults who have been subjected to chemotherapy and/or adults who have suffered from cahexia, or weight loss due to chronic disease.

30. A dietary supplement comprising an orally ingestible combination of a peptide according to any one of claims 1 to 8 combination with a physiologically acceptable

carrier.

31. An antibody which binds to a peptide according to any one of claims 1 or 8.

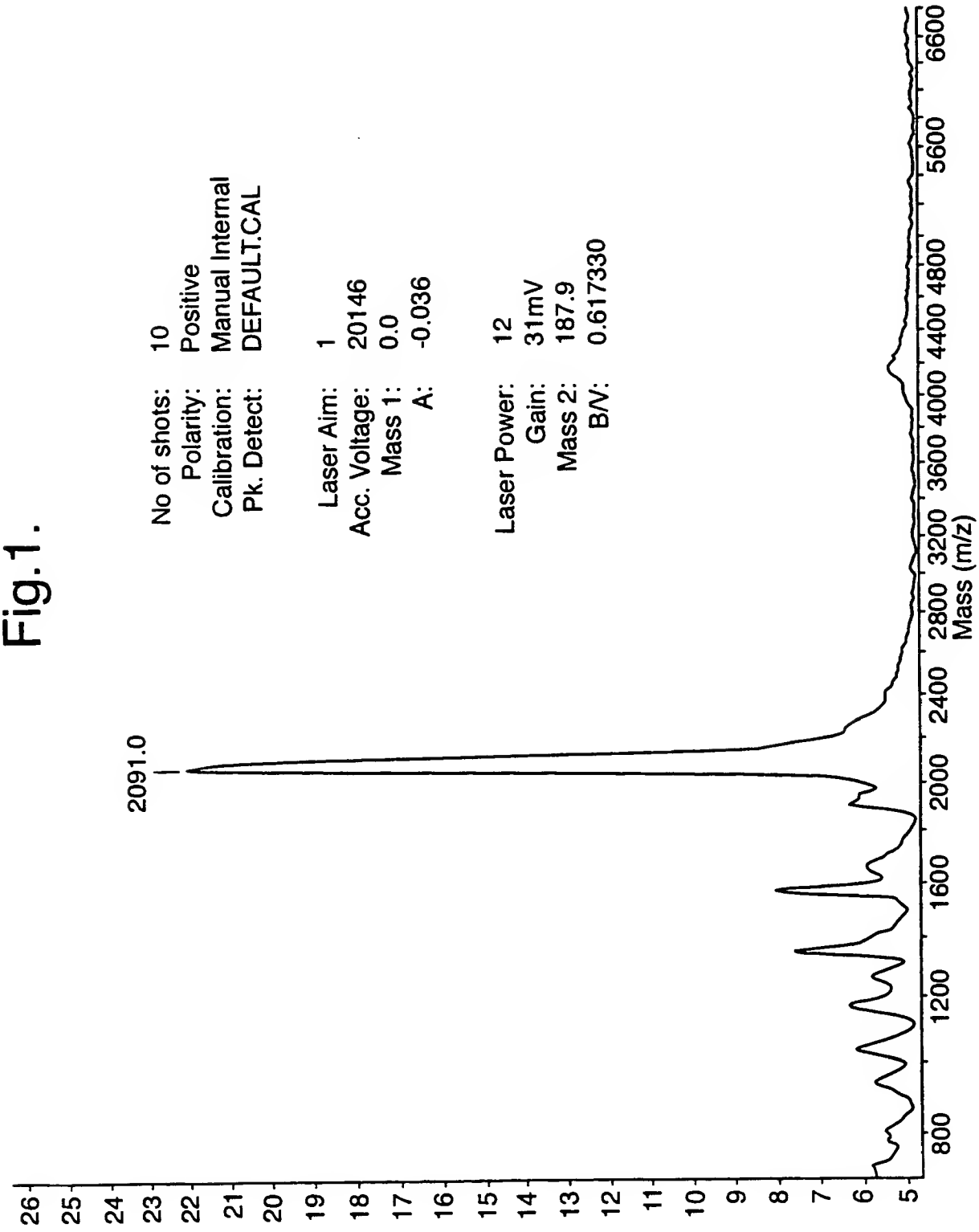
32. An antibody obtainable by using a peptide according to any one of claims 1 to 8 as an antigen.

33. A peptide containing the amino acid sequence LQTPQPLLQVMMEPQGD; DPPPPQS; and/or LFFFLPVVNVLP for use as an immunosuppressant.

34. A peptide containing the amino acid sequence LQTPQPLLQVMMEPQGD; DPPPPQS; and/or LFFFLPVVNVLP for use in the treatment of autoimmune disorder.

35. A peptide containing the amino acid sequence LQTPQPLLQVMMEPQGD; DPPPPQS; and/or LFFFLPVVNVLP for use in suppressing the rejection of transplanting organs.

Fig.1.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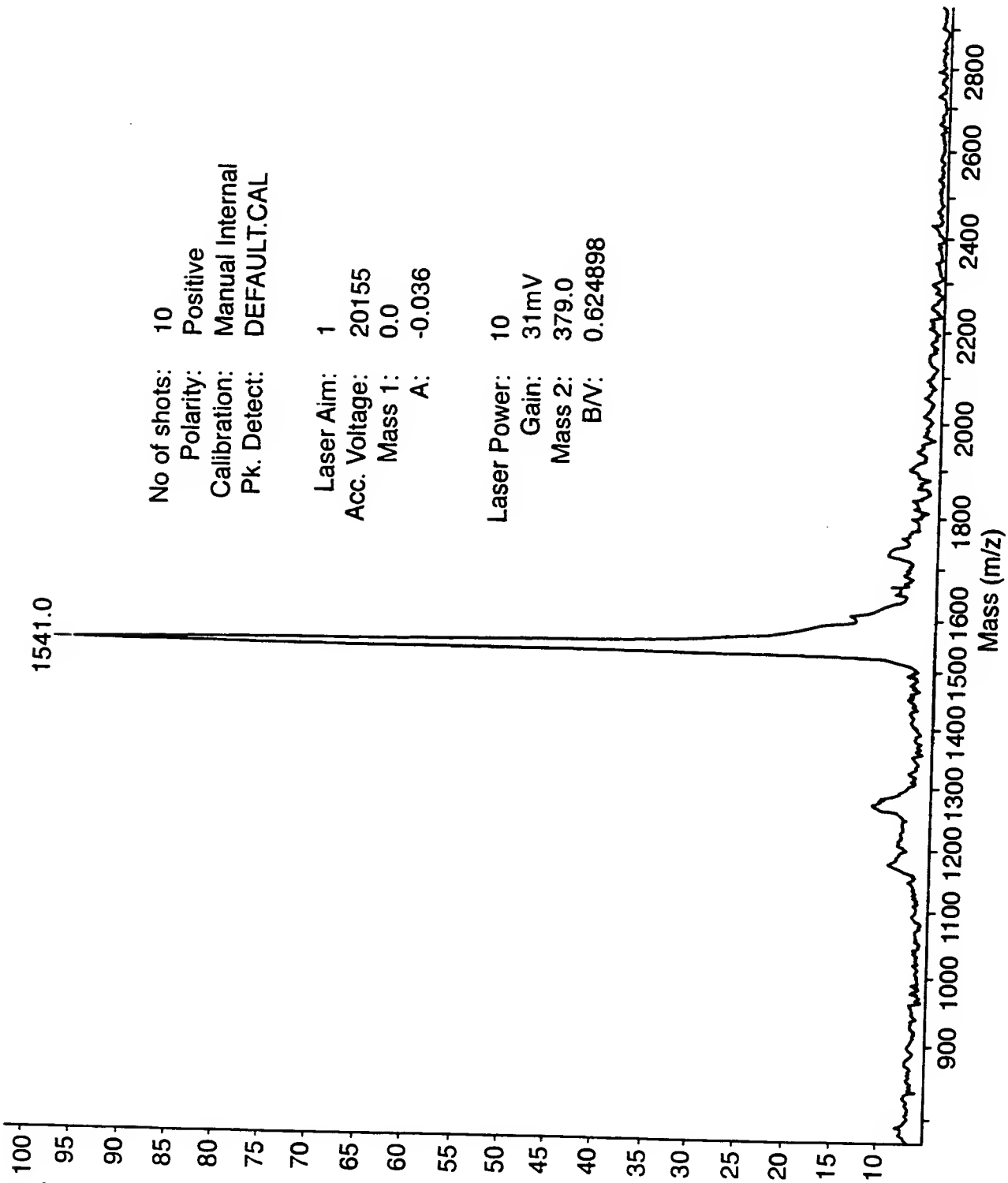
Mass (m/z)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Mass 2: 379.0
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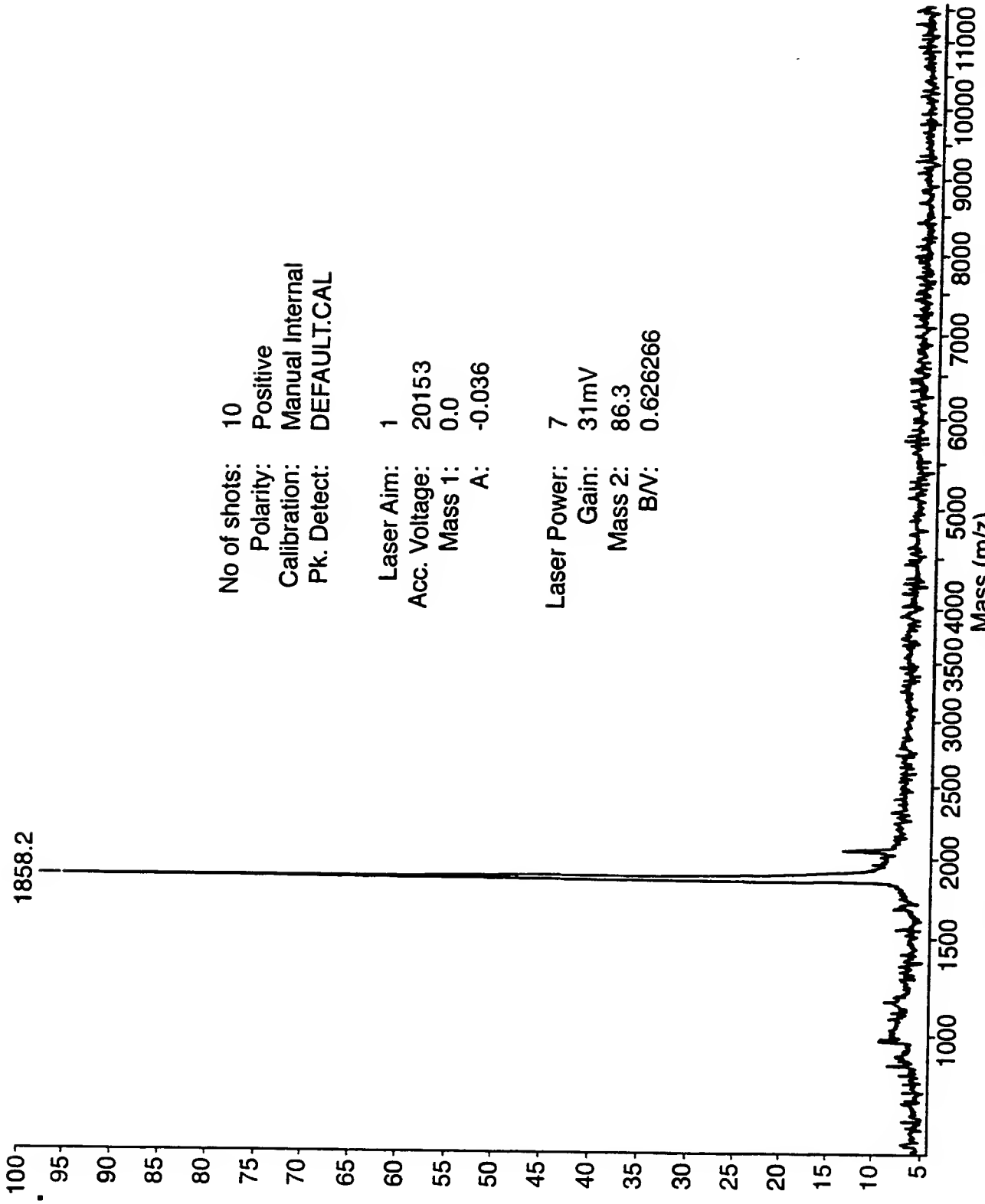
Mass (m/z)

Fig.2.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25
20
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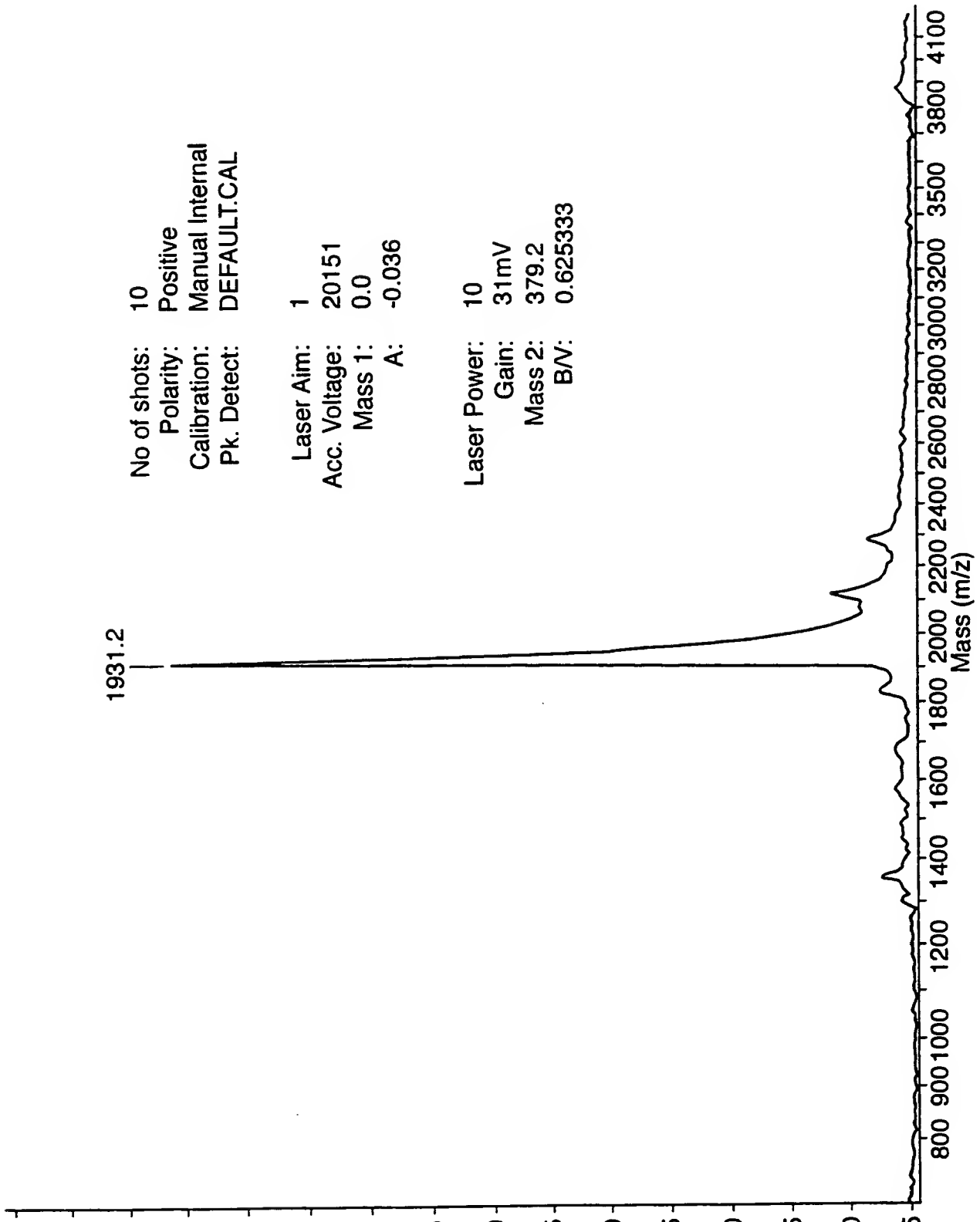
Mass (m/z)

Fig.3.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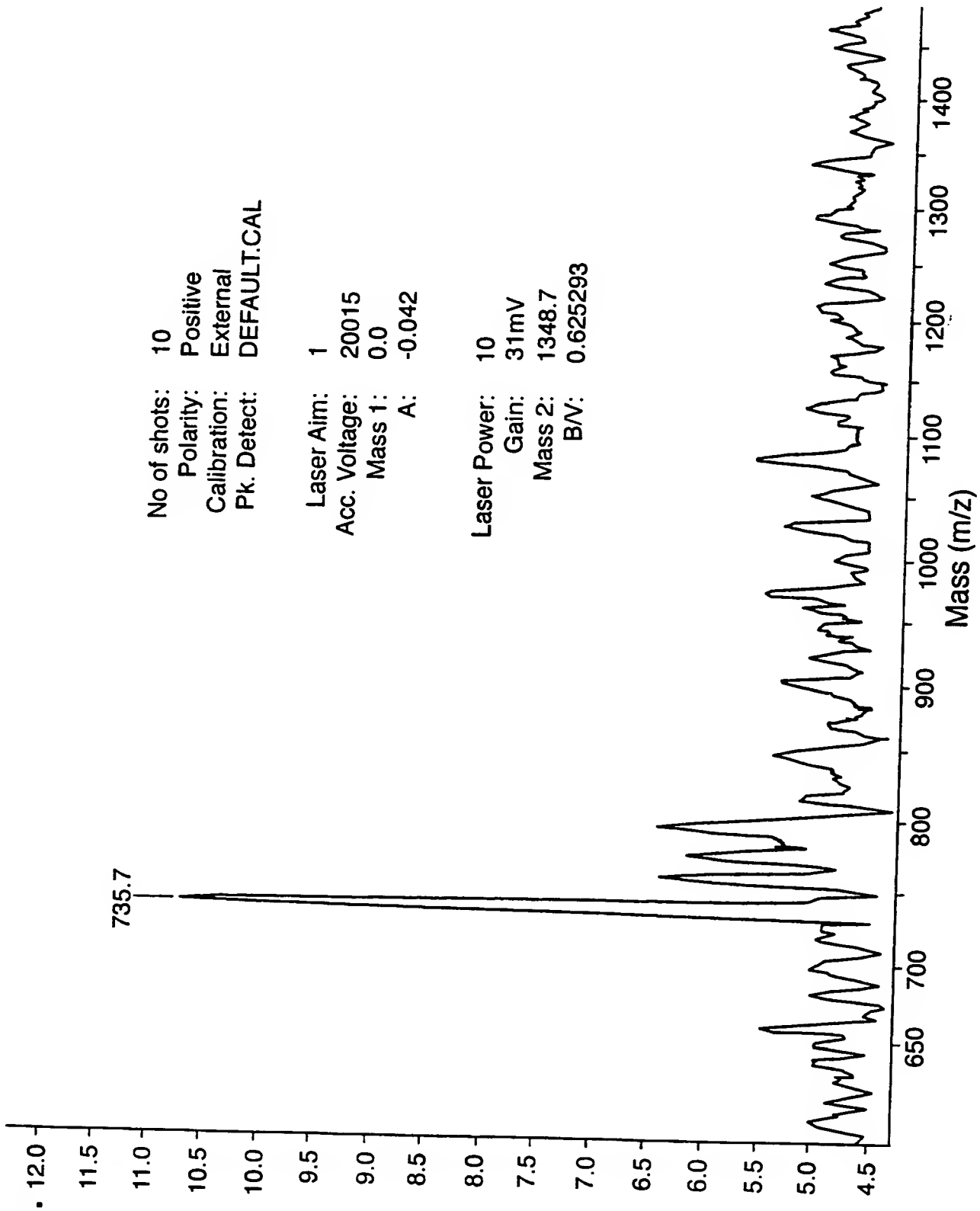
Mass 2: 379.2
B/V: 0.625333
1931.2
Mass (m/z)

Fig.4.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Laser Power: 10
Gain: 31mV
Mass 2: 1348.7
B/V: 0.625293
735.7
Mass (m/z)
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
650
700
800
900
1000
1100
1200
1300
1400

Fig.5.

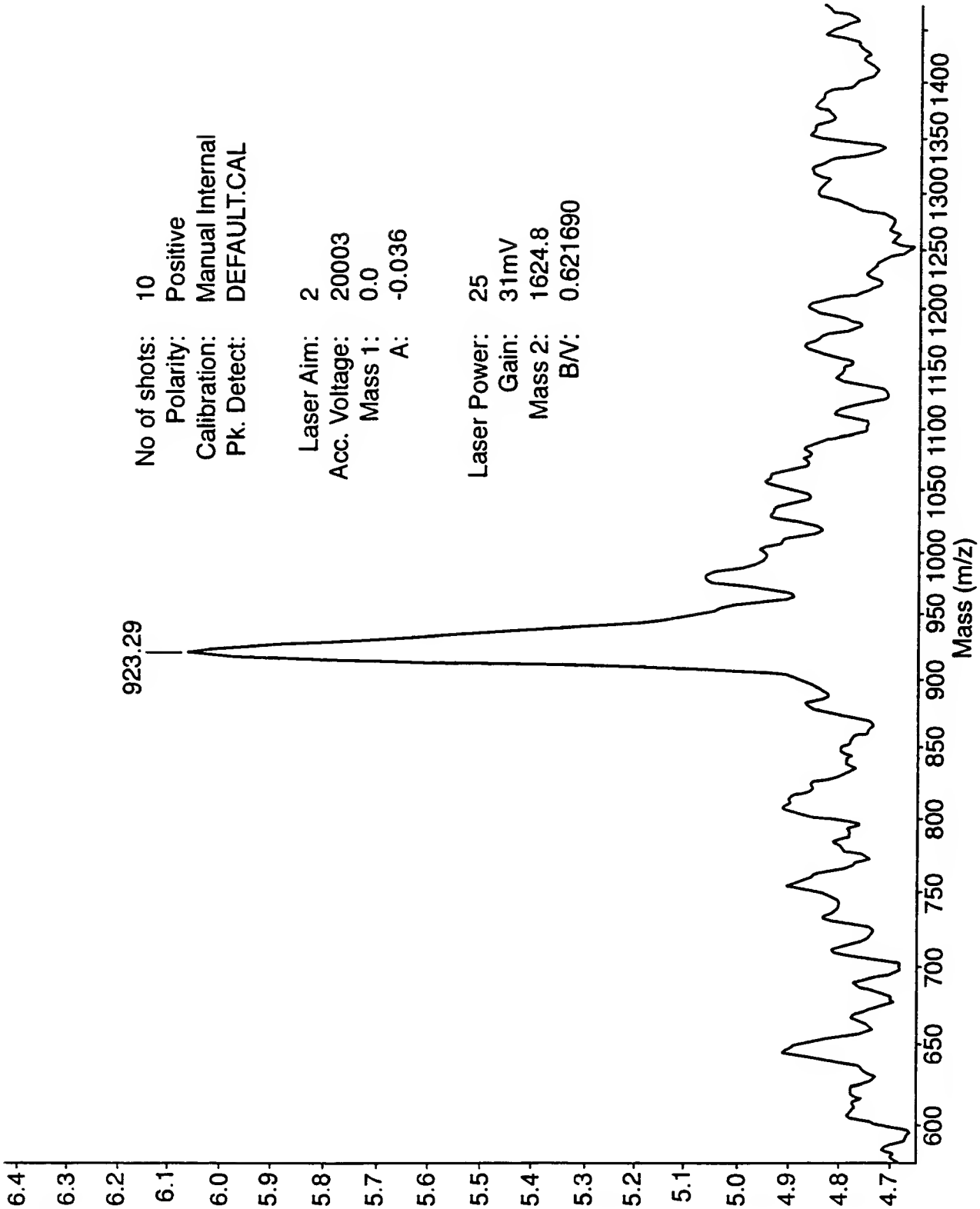

923.29
No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 2
Acc. Voltage: 20003
Mass 1: 0.0
A: -0.036
Laser Power: 25
Gain: 31mV
Mass 2: 1624.8
B/V: 0.621690
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7
600 650 700 750 800 850 900 950 1000 1050 1100 1150 1200 1250 1300 1350 1400
Mass (m/z)

Fig.6.

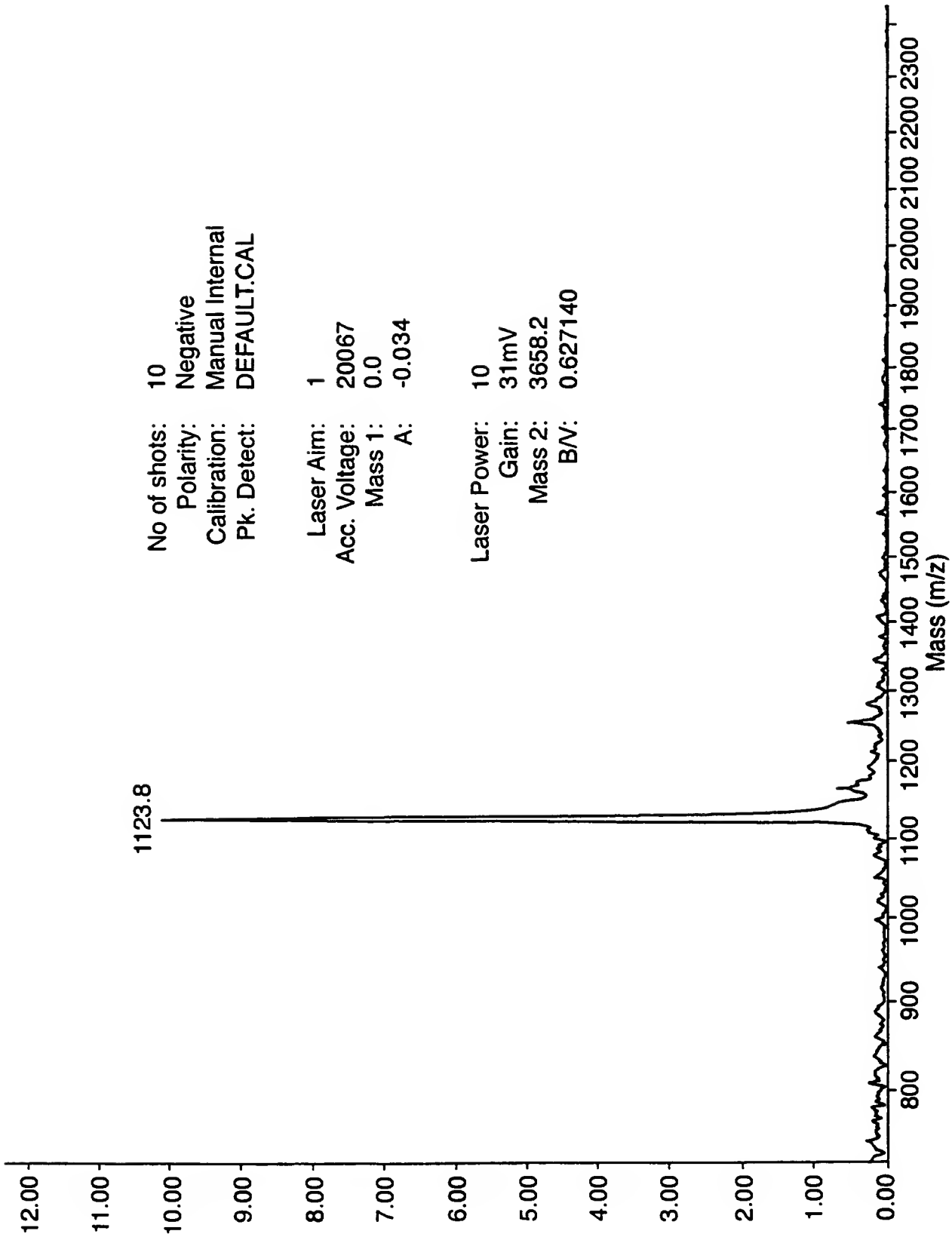

1123.8
No of shots: 10
Polarity: Negative
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20067
Mass 1: 0.0
A: -0.034
Laser Power: 10
Gain: 31mV
Mass 2: 3658.2
B/V: 0.627140
12.00
11.00
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300
Mass (m/z)

Fig.7.

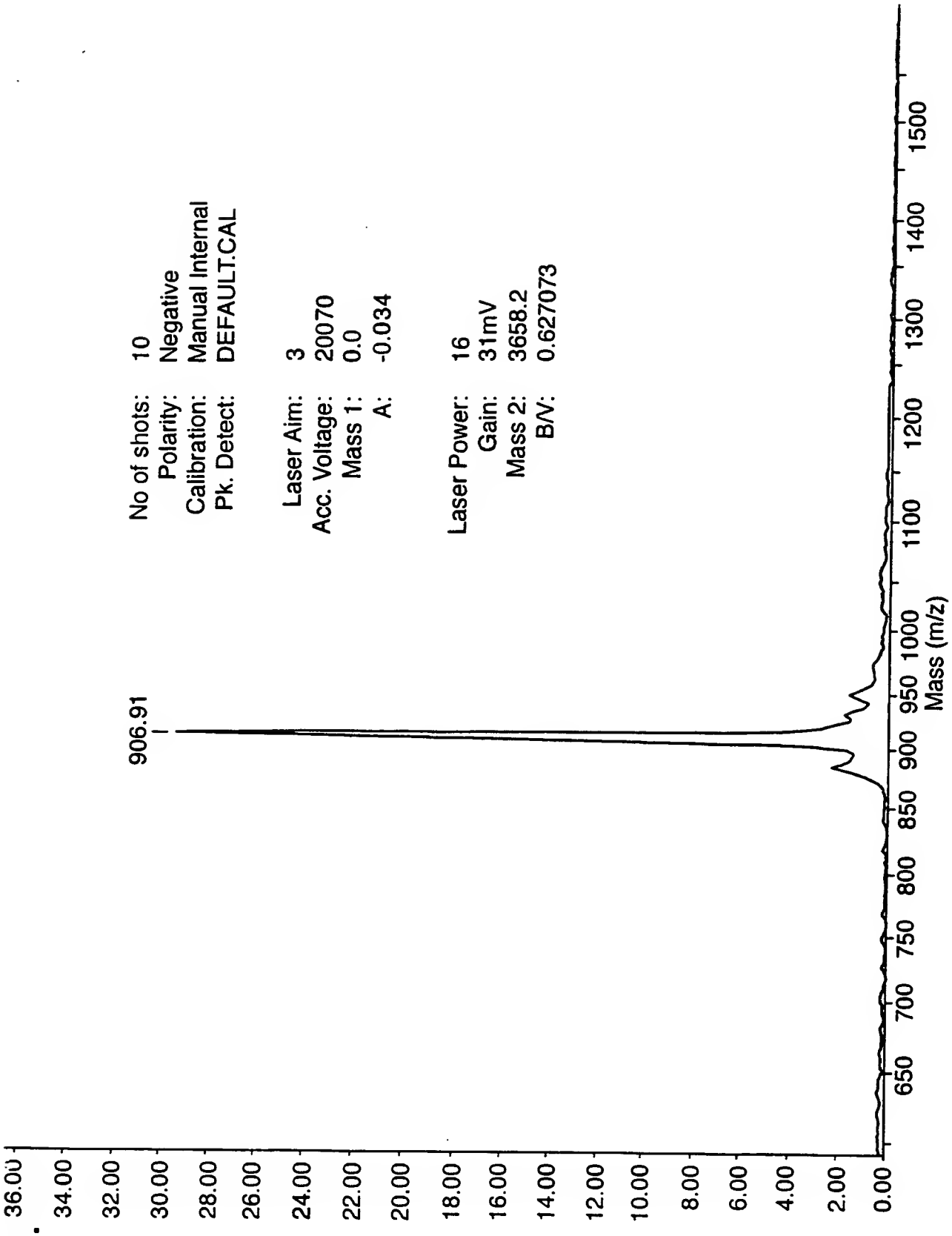

906.91
No of shots: 10
Polarity: Negative
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 3
Acc. Voltage: 20070
Mass 1: 0.0
A: -0.034
Laser Power: 16
Gain: 31mV
Mass 2: 3658.2
B/V: 0.627073
36.00
34.00
32.00
30.00
28.00
26.00
24.00
22.00
20.00
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
650
700
750
800
850
900
950
1000
1100
1200
1300
1400
1500
Mass (m/z)

Fig.8.

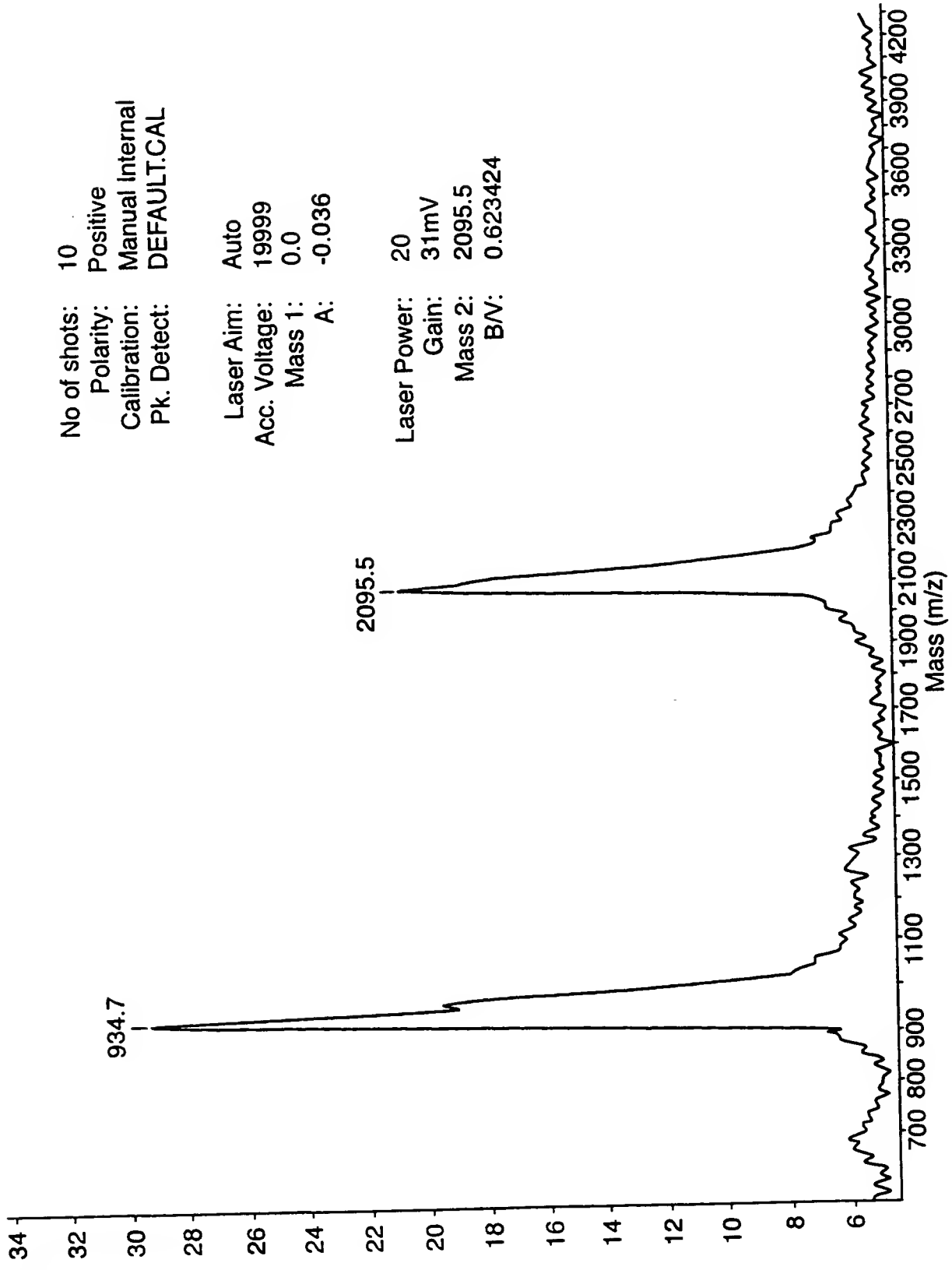

No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: Auto
Acc. Voltage: 19999
Mass 1: 0.0
A: -0.036
Laser Power: 20
Gain: 31mV
Mass 2: 2095.5
B/V: 0.623424
934.7
2095.5
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
700 800 900 1100 1300 1500 1700 1900 2100 2300 2500 2700 3000 3300 3600 3900 4200
Mass (m/z)

Fig.9.

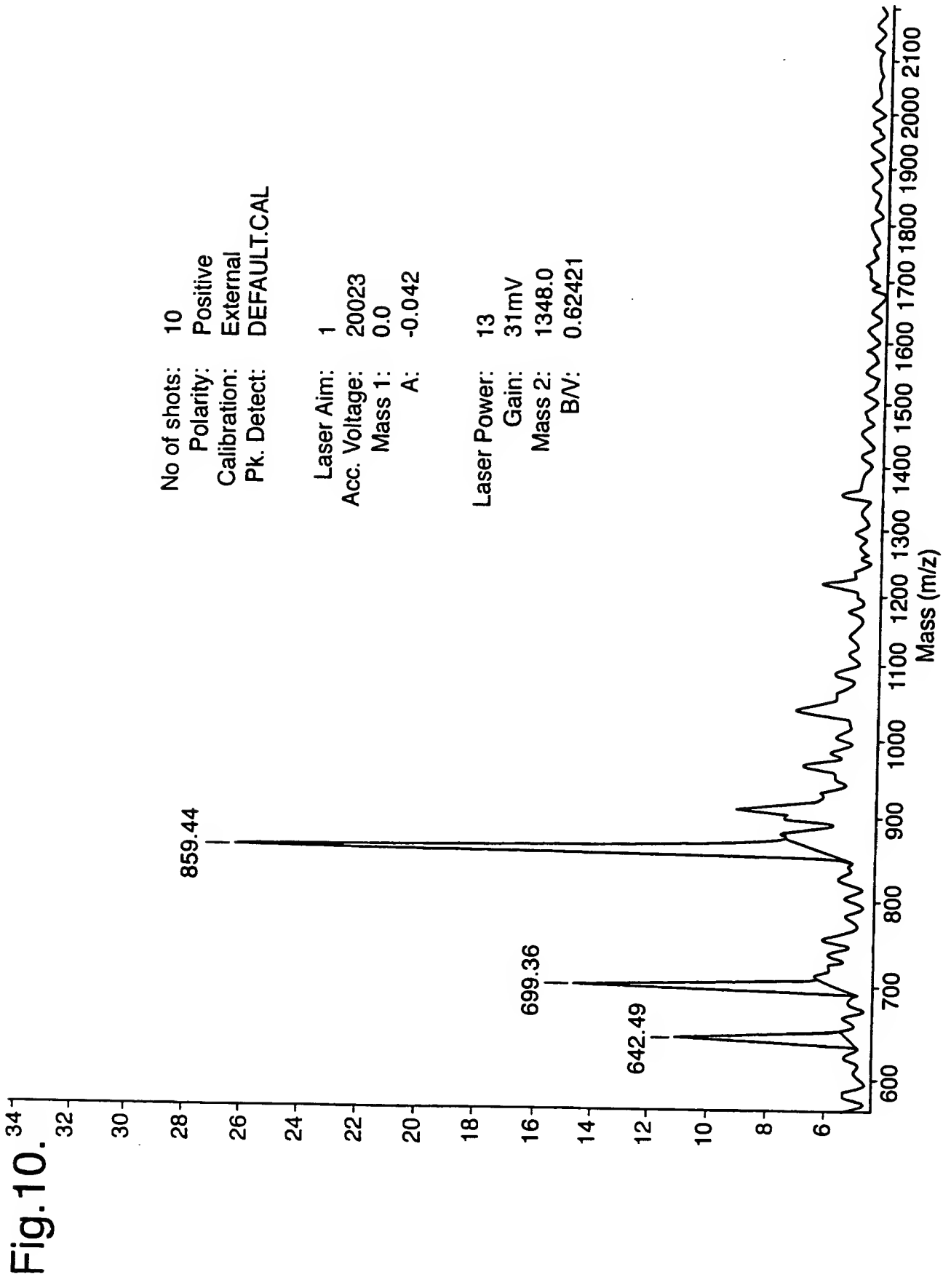

No of shots: 10
Polarity: Positive
Calibration: External
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20023
Mass 1: 0.0
A: -0.042
Laser Power: 13
Gain: 31mV
Mass 2: 1348.0
B/V: 0.62421
859.44
699.36
642.49
Mass (m/z)

Fig.10.

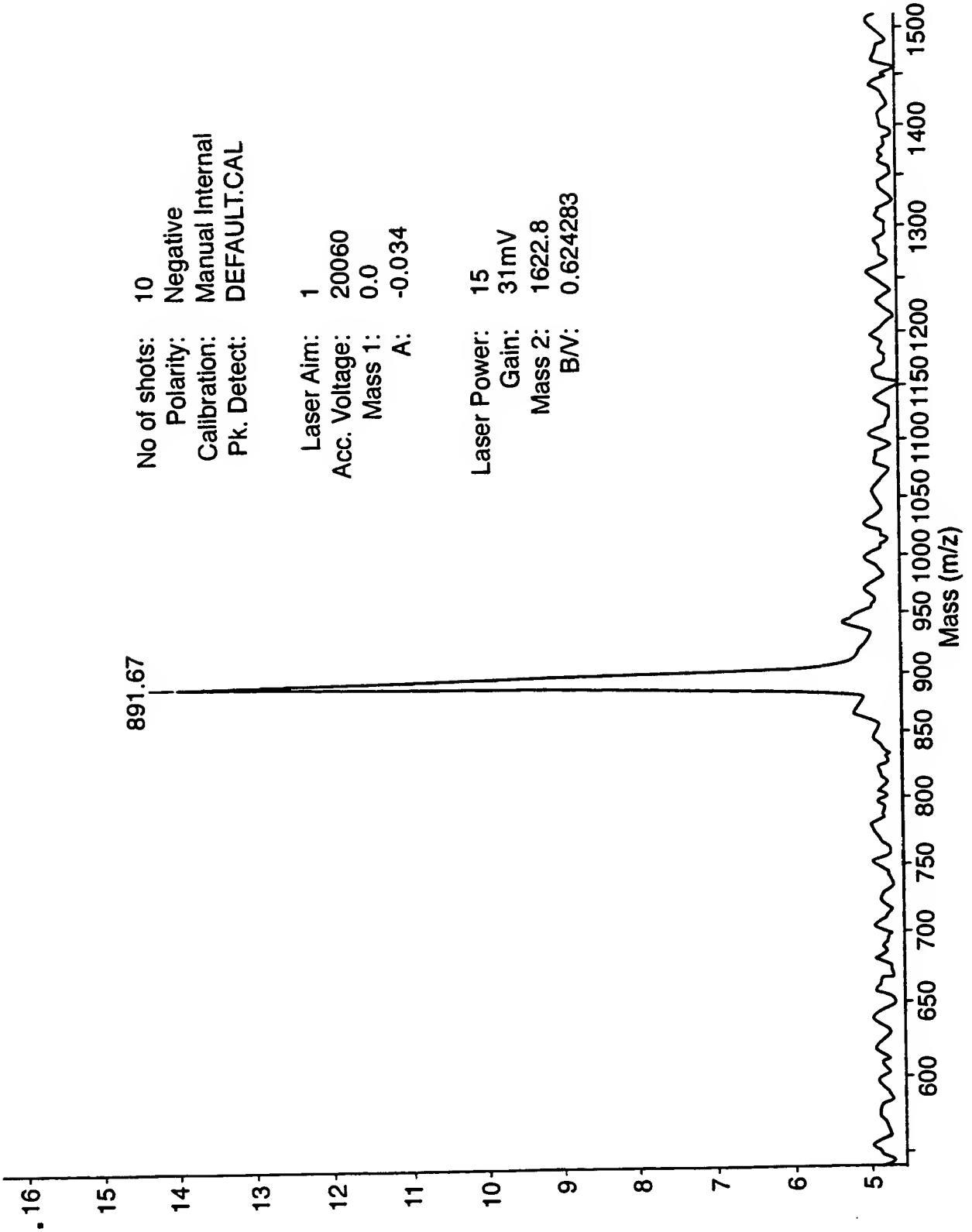

No of shots: 10
Polarity: Negative
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20060
Mass 1: 0.0
A: -0.034
Laser Power: 15
Gain: 31mV
Mass 2: 1622.8
B/V: 0.624283
891.67
16
15
14
13
12
11
10
9
8
7
6
5
600 650 700 750 800 850 900 950 1000 1050 1100 1150 1200 1300 1400 1500
Mass (m/z)

Fig.11.

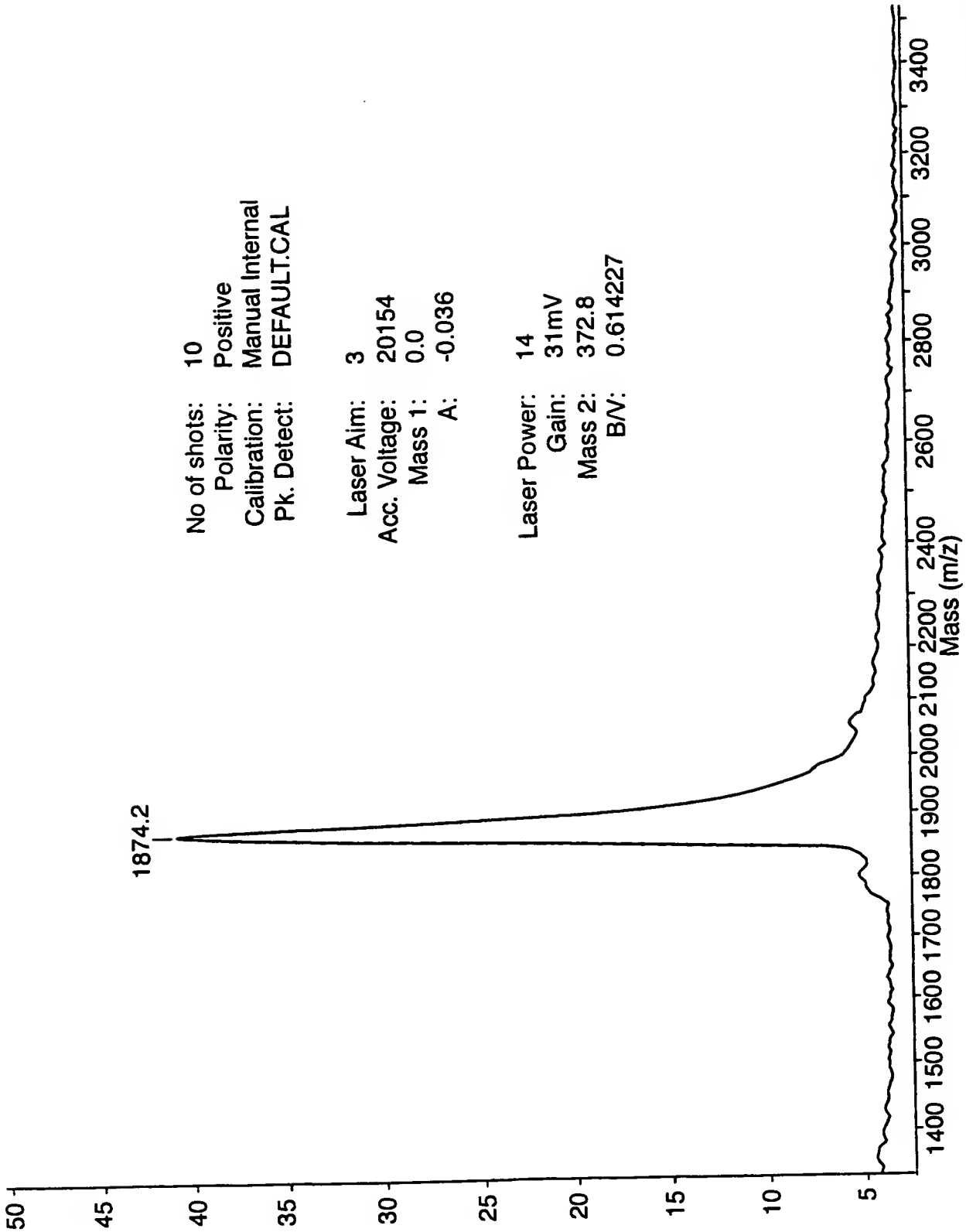
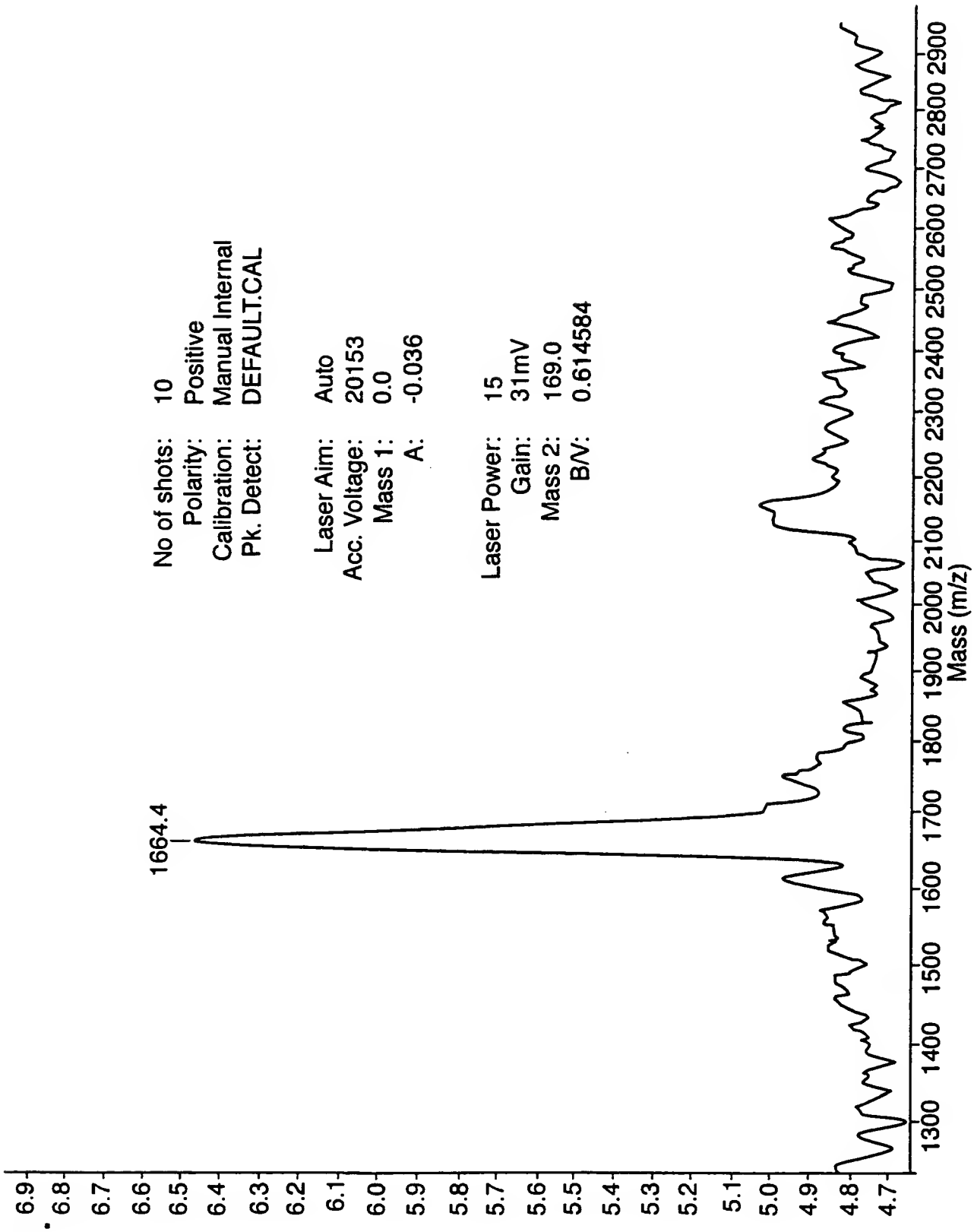

No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 3
Acc. Voltage: 20154
Mass 1: 0.0
A: -0.036
Laser Power: 14
Gain: 31mV
Mass 2: 372.8
B/V: 0.614227
1874.2
50
45
40
35
30
25
20
15
10
5
1400 1500 1600 1700 1800 1900 2000 2100 2200 2400 2600 2800 3000 3200 3400
Mass (m/z)

Fig.12.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No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: Auto
Acc. Voltage: 20153
Mass 1: 0.0
A: -0.036
Laser Power: 15
Gain: 31mV
Mass 2: 169.0
B/V: 0.614584
Mass (m/z)
1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300 2400 2500 2600 2700 2800 2900
4.7 4.8 4.9 5.0 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8 5.9 6.0 6.1 6.2 6.3 6.4 6.5 6.6 6.7 6.8 6.9

Fig.13.

Fig.14.

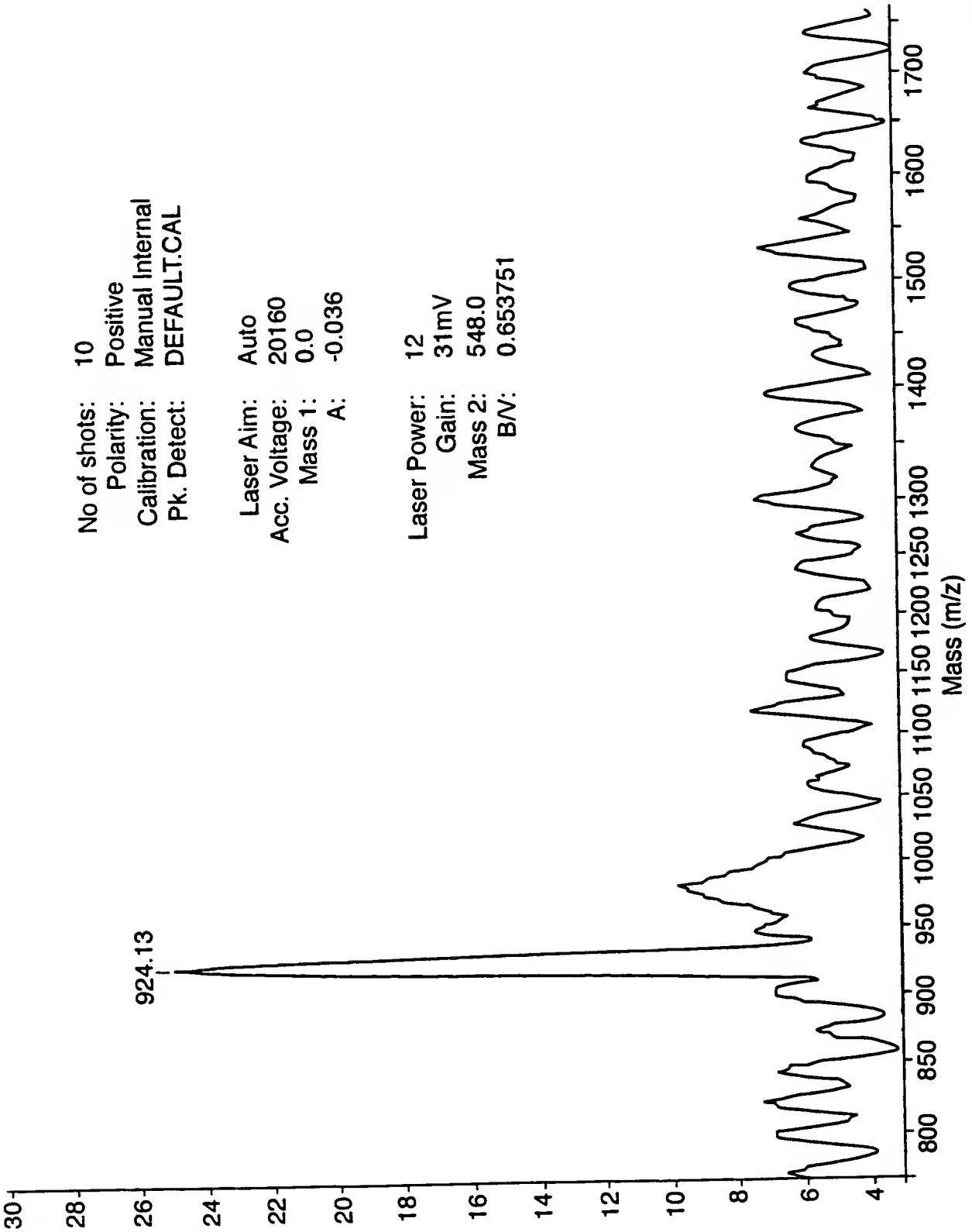
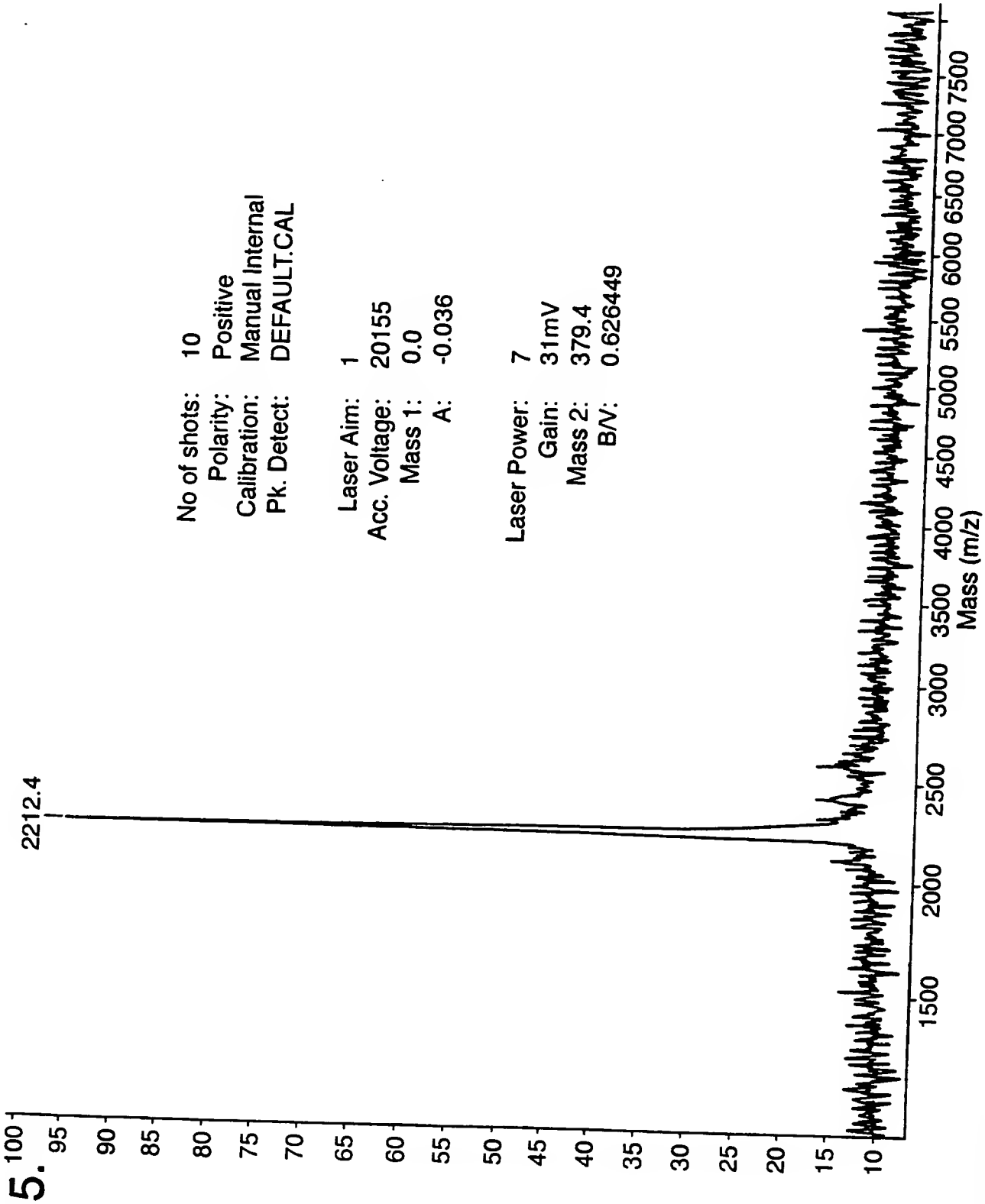

No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: Auto
Acc. Voltage: 20160
Mass 1: 0.0
A: -0.036
Laser Power: 12
Gain: 31mV
Mass 2: 548.0
B/V: 0.653751
924.13
30
28
26
24
22
20
18
16
14
12
10
8
6
4
800 850 900 950 1000 1050 1100 1150 1200 1250 1300 1400 1500 1600 1700
Mass (m/z)

Fig.15.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No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20155
Mass 1: 0.0
A: -0.036
Laser Power: 7
Gain: 31mV
Mass 2: 379.4
B/V: 0.626449
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
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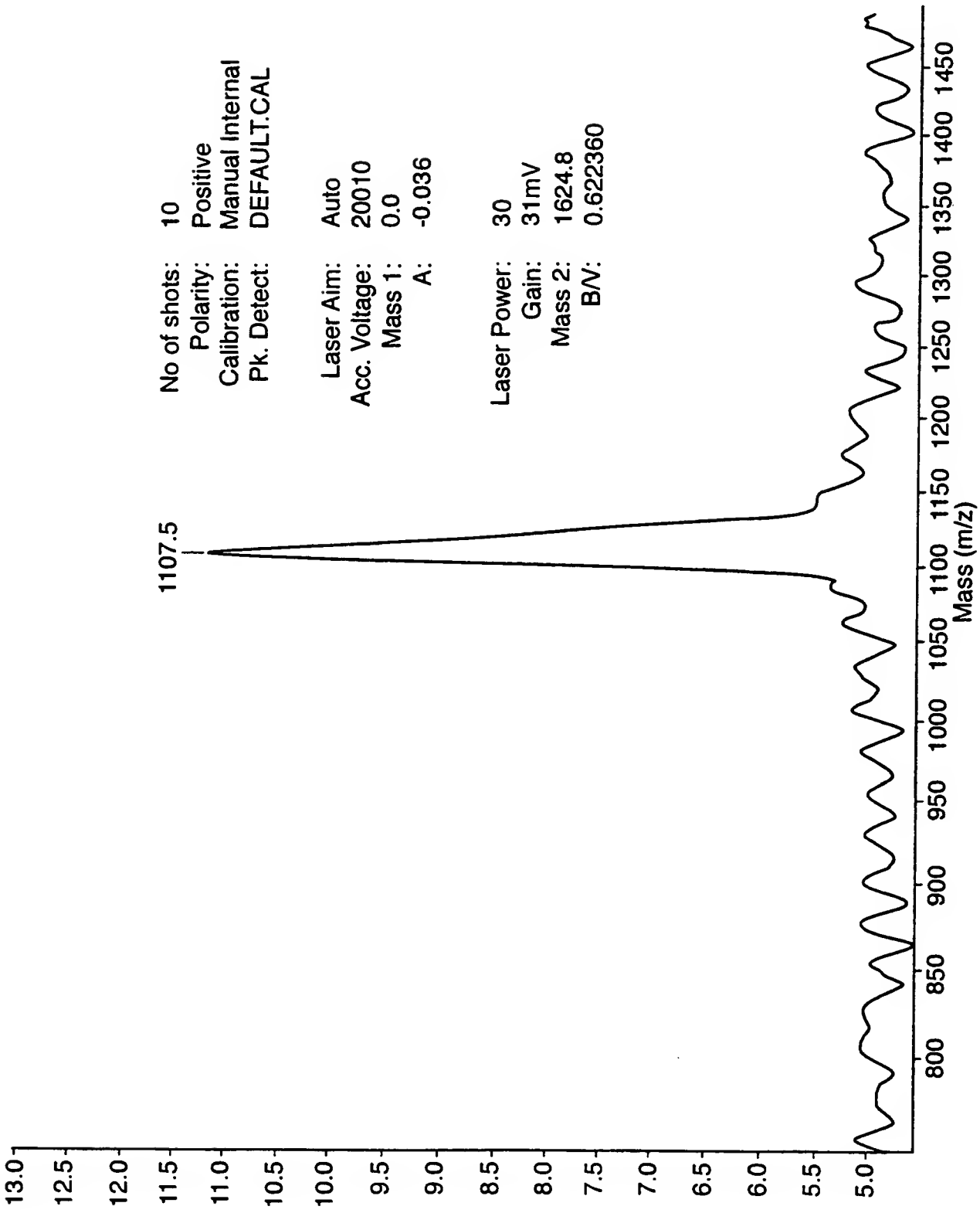
2000
2500
3000
3500
4000
4500
5000
5500
6000
6500
7000
7500
Mass (m/z)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No of shots: 10
Polarity: Positive
Calibration: Manual Internal
Pk. Detect: DEFAULT.CAL
Laser Aim: Auto
Acc. Voltage: 20010
Mass 1: 0.0
A: -0.036
Laser Power: 30
Gain: 31mV
Mass 2: 1624.8
B/V: 0.622360
Mass (m/z)
800 850 900 950 1000 1050 1100 1150 1200 1250 1300 1350 1400 1450
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0

Fig.16.

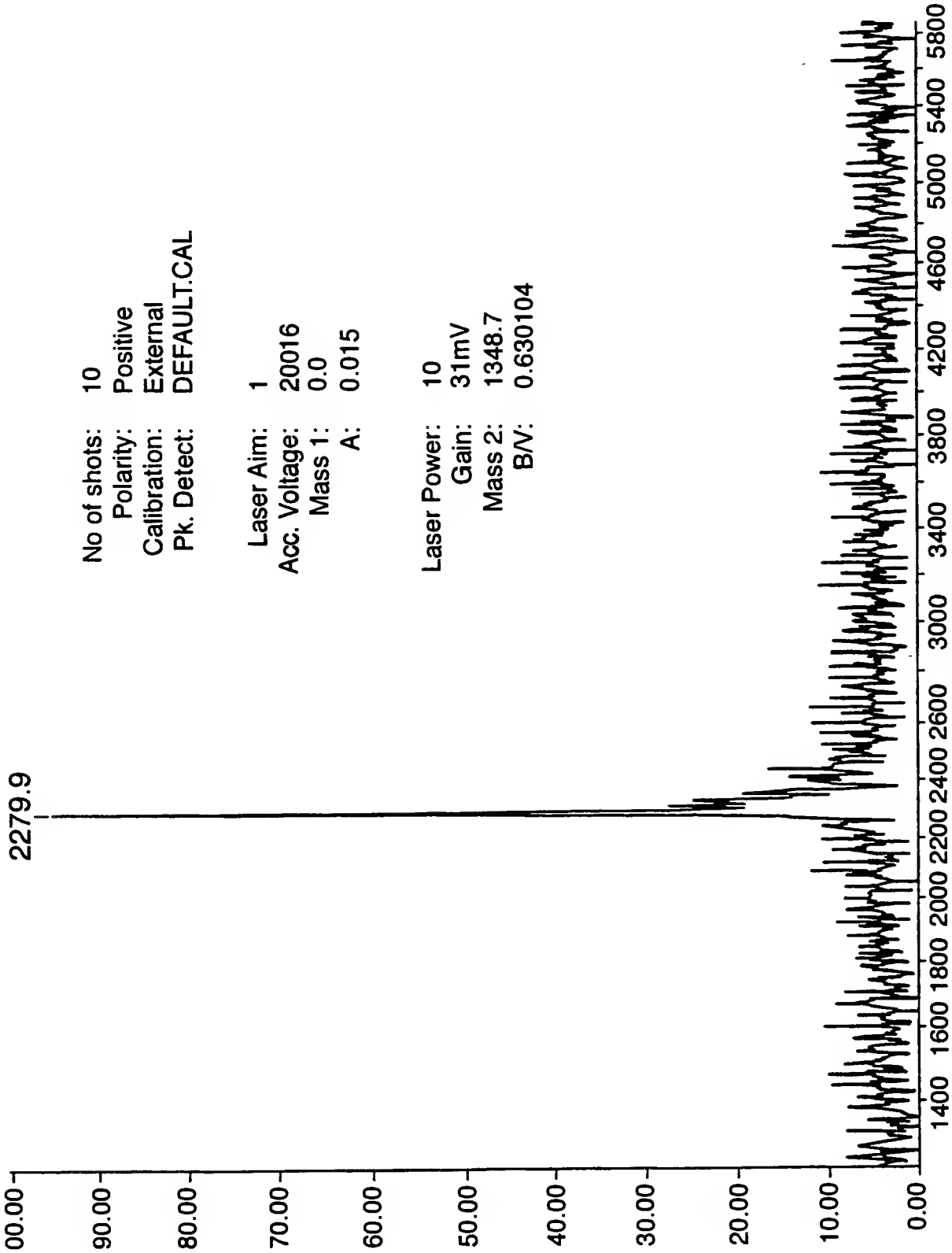
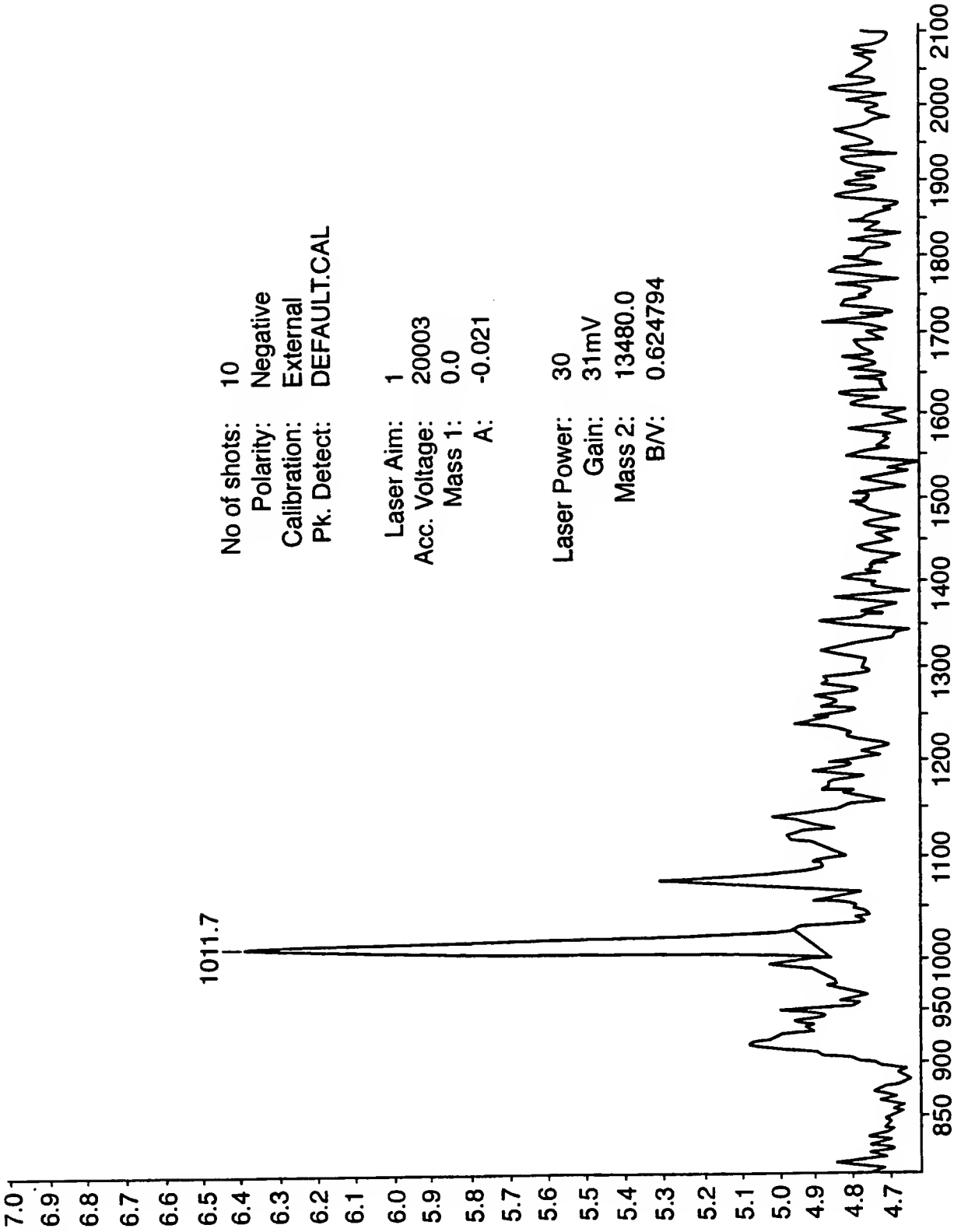

2279.9
No of shots: 10
Polarity: Positive
Calibration: External
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20016
Mass 1: 0.0
A: 0.015
Laser Power: 10
Gain: 31mV
Mass 2: 1348.7
B/V: 0.630104
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
1400 1600 1800 2000 2200 2400 2600 3000 3400 3800 4200 4600 5000 5400 5800
Mass (m/z)

Fig.17.


No of shots: 10
Polarity: Negative
Calibration: External
Pk. Detect: DEFAULT.CAL
Laser Aim: 1
Acc. Voltage: 20003
Mass 1: 0.0
A: -0.021
Laser Power: 30
Gain: 31mV
Mass 2: 13480.0
B/V: 0.624794
1011.7
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
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Mass (m/z)

Fig.18.

SEQUENCE LISTING

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<170> PatentIn Ver. 2.1

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Asp

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Val Leu Glu Met Lys Phe Pro Pro Pro Pro Gln Glu Thr Val Thr
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<210> 9
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isolated from colostrinin

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isolated from colostrinin

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Gln Ser

<210> 19
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<210> 20
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<210> 22
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isolated from colostrinin

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Pro Lys

<210> 23
<211> 18
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isolated from colostrinin

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Ser Gln

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isolated from colostrinin

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Val Gln

<210> 25
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isolated from colostrinin

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<210> 26
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isolated from colostrinin

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isolated from colostrinin

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<210> 28
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isolated from colostrinin

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<210> 29
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isolated from colostrinin

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Arg Asp Met Pro Ile Gln
20

<210> 30
<211> 7
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<220>

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<210> 31
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<210> 32
<211> 8
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<210> 33
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Ser Leu

<210> 34
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isolated from colostrinin

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1 5 10 15

Gly Asp

<210> 35
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isolated from colostrinin

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<210> 36
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isolated from colostrinin

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<210> 37
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<210> 38
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<210> 39
<211> 9
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<220>
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1 5

<210> 40
<211> 10
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1 5 10

<210> 41
<211> 9
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<210> 43
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<210> 44
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<210> 45
<211> 16
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<210> 46
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isolated from colostrinin

<400> 46
Cys Leu Phe Phe Phe Leu Pro Val Val Asn Val Leu Pro Ile
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<210> 47
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<220>
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isolated from colostrinin

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Cys Met Gln Pro Pro Pro Leu Pro
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<210> 48
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<223> Description of Artificial Sequence: Peptide
isolated from colostrinin

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Cys Asp Gln Pro Pro Asp Val Glu Lys Pro Asp Leu Gln Pro Phe Gln
1 5 10 15

Val Gln Ser

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isolated from colostrinin

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Cys Gly Ala Phe Leu Leu Tyr Gln Glu

1 5

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<220>
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isolated from colostrinin

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1 5 10 15

Lys Ser Leu